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BIOCHEMICAL ASPECTS OF SCHIZOPHRENIA

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The cause of schizophrenia is as little understood in a basic sense today as were infectious diseases before the time of Pasteur. Whether schizophrenia is one disease or many is unclear. Psychiatrists are able to diagnose cases as schizophrenia with some consistency on a characteristic set of behavior abnormalities. These abnormalities tend to be relatively culture-free in a sense that schizophrenics from London, or from the Fiji Islands or from Oshkosh display similar constellations of abnormal behaviors patterns. To biochemists and physiologists interested in the psychoses, it is a working hypothesis that these people are no less physically ill than are persons with arthritis or influenza. The behaving of a disembodied psyche is a meaningless concept. Abnormal behavior is presumed to indicate abnormal brain function. The fact that such disturbances are undetectable by the relatively crude microtechniques of histology in no way militates against the view of the dependence of schizophrenia on subtle changes of molecular dynamics in tissues of the brain or its internal environment.

In the following discussion we shall review some recent hypotheses of possible biochemical determinants of the psychoses. Work in this field has been considerably facilitated during recent years by the discovery of drugs that produce transient experimental psychoses in normal human subjects, and we shall consider among other things some recent contributions resulting from the study of some of these drugs.

For a half century there has been controversy as to whether schizophrenia is ordinarily a result of disturbances in physicochemical events in the nervous system, or whether it is psychogenic in origin. Work of geneticists in recent years has helped clarify this problem and data of Franz Kallmann (13) are of special interest in this connection. He has studied the incidence of schizophrenia in approximately 5800 relatives of hospitalized schizophrenic patients whose diagnoses were agreed upon by competent psychiatrists. The group of relatives included 268 one-egg identical twins and 685 two-egg twins.

Kallmann's data, in round numbers, indicate that the expectancy of schizophrenia in the population at large in the United States is 1 per cent. If, however, there is one schizophrenic parent in a family, the expectancy that there will be at least one schizophrenic offspring is increased to 16 per cent. With two schizophrenic parents, the expectancy of a schizophrenic child becomes 68 per cent. If one sibling, other than an identical twin, is schizophrenic in a family the probability that another one will be is 14 per cent. These results could be interpreted either as due to genetic factors predisposing to vulnerability or to social conditioning acting psychologically

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to promote psychoses. However, his further data on the incidence of schizophrenia in twins appear to be susceptible only to a genetic interpretation. Thus, any twins born at the same time are usually brought up in closer emotional rapport with each other than are ordinary siblings separated by years in time of birth, but two-egg twins have as different a genetic makeup as do two children of the same parents born at different times. Therefore, if biologic factors are predisposing ones for schizophrenia, the situation should be similar for two-egg twins as it is for any siblings in a family born at different times, and indeed this was found to be the case. The expectancy, if one two-egg twin is schizophrenic that the other will be is also 14 per cent. If, however, one turns to the 268 identical one-egg twins, in which each member of the pair has the same genes, one finds that the expectancy goes up to 86 per cent. Despite the fact that some members of the twin pairs were reared apart from infancy, the expectancy was of this same magnitude. This clearly demonstrates, and such results have been confirmed by others, that there exists a predisposing genetic factor in the face of life's stresses making for vulnerability leading to the development of schizophrenia. Work of geneticists with lower organisms has established that the genes are templates responsible for the production of the specific enzymes that guide the course of cellular metabolism in all the cells of the body. This being the case, metabolic abnormalities resulting from abnormal gene determined enzyme synthesis, might be expected to be reflected in aberrant intermediate metabolites detectable in blood, urine, and cerebrospinal fluid, of schizophrenic patients in contrast to metabolites in the fluids of nonpsychotic persons.

An interesting prototype to illustrate this point is displayed by the disorder of oligophrenia or phenylketonuria. Persons suffering from this disease are invariably feebleminded. Oligophrenia appears to be due to the defect of one gene inherited recessively which causes the lack of a specific enzyme needed to convert the aminoacid phenylalanine to tyrosine. Because of this enzyme deficiency, phenylalanine cannot be converted to the normal intermediate metabolite dihydroxyphenylpyruvic acid. As a consequence, phenylpyruvic acid is formed and excreted in the urine. If urinary tests for this substance are aplied to very young infants in families suspected of carrying the genetic deficit, the condition of oligophrenia is readily diagnosed. Under such circumstances, if the infant receives no milk or other foods containing phenylalanine but is given instead food with the essential amino acids but lacking phenylalanine, the child may develop normally as long as the diet is strictly adhered to. In oligophrenia we have a direct relation between a genetic deficit resulting in a molecular lesion as a failure in enzyme formation with consequent deflections of intermediary metabolism resulting in mental deficiency. Whatever the genetic deficiency is in schizophrenia it is probably more complicated and may involve a number of genes and enzyme systems. Nevertheless, search for metabolic disturbances as reflected in body fluids of schizophrenics would appear to be a sound approach for detecting what may be important causal clues to the disorder, clues which may lead ultimately to a rational chemotherapy in contrast to the empirical hit or miss, shotgun procedures hitherto employed as therapies for this disorder.

It should be pointed out that these considerations do not necessarily imply a single biochemical lesion in schizophrenia, though this may be so for oligophrenia. Few if any diseases have single causes. Genetic vulnerability may be countered therapeutically as in oligophrenia, diabetes, cardiovascular disorders and many other conditions in which one finds significant familial trends. That such diverse therapies as psychotherapy, shock, lobotomy and tranquil-

izers can affect the schizophrenic process in a limited number of patients argues for a multiplicity of factors involved in the disorder. But this in no way militates against the view that certain critical biochemic lesions may be predominant as insidious factors leading to psychoses in response to life's stresses.

A search of some interest for biochemical defects has involved the investigation of the properties of amines, which play a role in brain function. Mescaline (β.3.4.5. trimethoxyphenylethylamine) is an amine which produces visual hallucinations and bizarre psychiatric experiences. It has been used by Indians of our Southwest for centuries to produce mystic experiences in connection with their religious rites. The structural similarity of this substance to the hormone adrenaline led Osmond and Smythies in 1952 (16) and Hoffer, Osmond and Smythies in 1954 (12) to suggest that a disturbance in the metabolism of adrenaline might result in agents capable of producing endogenous psychoses. They note that Lindemann in 1935 reported that adrenaline administration exacerbates psychotic symptoms in some schizophrenic patients. Hoffer *et al.* cited a few cases in which persons receiving adrenaline for therapeutic reasons experienced unusual psychiatric reactions. In normal persons, adrenaline produces a sort of free-floating experience of anxiety, during its relatively short time of action. Axelrod (5) isolated from urine of rats methoxyadrenaline and Gaudette and Scott (8) in our laboratory using administered C14 labelled adrenaline and chromatographic procedures found 3-methoxyadrenaline and 3-methoxy 4-hydroxy mandelic acid in urine of rabbits. Thus methylation to form mescaline-like structures occurs and is now under investigation in schizophrenic and normal men.

In vitro oxidation of adrenaline has resulted in the production of a number of relatively unstable products including the indoles adrenochrome and adrenolutin. Hoffer, Osmond and Smythies have reported from experiments conducted on themselves and on their colleagues that both adrenochrome (12) and adrenolutin (10) produce when intravenously injected, psychotomimetic effects in normal persons. This work, however, has not been confirmed. These substances do however produce bizarre effects on animal behavior.

Adrenochrome has not been found as an intermediate metabolite of adrenaline *in vivo*, but this may not be surprising because of its marked instability. It may be continually formed and inactivated and as an intermediate elude detection especially if produced at nerve endings or in highly specific loci. There are enzymes present capable of metabolizing it. *In vitro* studies have shown that adrenochrome interferes with oxidative phosphorylation and with the activity of sulfhydryl enzymes in brain mitochondria. Abood (1) reports that oxidation products of amines such as adrenaline, tyrosine and dihydroxyphenylalanine yield aldehydes and ketones that have powerful inhibitory effects on these brain enzymes. Thus, adrenochrome in concentrations of 5×10^{-5} M has a 50 per cent blocking action on oxidative phosphorylations in brain mitochondria. But most of these intermediate metabolites in the body are readily destroyed by monoamine oxidase in the cells and by a copper-containing blood enzyme known as ceruloplasmin (CLP).

Leach and Heath (14) have shown that schizophrenic serum contains enzymes which primarily oxidize added adrenaline at a faster rate than occurs in normal serum, but this effect is nonspecific since more rapid adrenaline oxidation occurs in serum from cancer cases, normal pregnancy cases and from patients suffering from a variety of other illnesses. Oxidation of adrenaline is also not specific since a great variety of other amines are also oxidized by CLP. However, the schizophrenic serum seems to have an unusually high amine de-

stroying capacity. Ceruloplasmin is composed of an α-globulin with a copper prosthetic group and has a molecular weight of about 160,000. It contains 96 per cent of the copper in the blood. Scheinberger *et al.* (18) have found the CLP content of schizophrenic plasma to be significantly higher than that of normal persons but there is much overlap; high values of this enzyme are also found in cases of liver disease, pregnancies, malignancies and myocardial infarction. The rate of oxidation of amines by blood is a resultant of the oxidizing potential of the CLP and the reducing actions of blood ascorbic acid and glutathione and some other less active reducing agents in the plasma. Studies of Akerfeldt (3) on the oxidation of N-N dimethylparaphenylenediamine have indicated that the slower oxidation of this substance by normal human serum in comparison with the more rapid oxidation of serum from schizophrenic patients is due to the fact, known for some time, that the schizophrenic serum contains less ascorbic acid. Heath and Leach, independently, have pointed out that the reducing agent glutathione is also low in schizophrenic blood and this would account in part for the accelerated rate of oxidation of adrenaline in schizophrenic serum. But the effects are not specific since amines are oxidized faster also in cases of pregnancies, malignancies and other diseases.

Adrenolutin, claimed by Hoffer and Osmond to be psychosis-inducing, may be formed in the course of oxidation of added adrenaline by enzymes in the blood, according to experiments of Hoffer and Kenyon (11). They used Heath's procedure of adding adrenaline to the serum of schizophrenic patients to produce oxidation products measurable by spectrophotometry. Leach and Heath had found that the main product formed after this oxidation had an absorption peak at a wave length of 395 mμ. Hoffer and Kenyon found that 1 minute after adding adrenaline to the serum there was no evidence of any new substance formed, but at the end of 80 minutes a product appeared having the same absorption peak of 395 mμ as that reported by Heath and Leach. Added adrenochrome after 1 minute also gave no evidence of new compound formation, but in 80 minutes adrenochrome had also formed a substance with an absorption peak at 395 mμ. Adrenolutin added to the serum, in 1 minute showed this same peak at 395 mμ which corresponded to the final oxidation products of adrenaline and adrenochrome. After 80 minutes the peak for adrenolutin had not changed suggesting that adrenolutin is the final compound formed by enzyme oxidation in the blood of adrenaline and also of adrenochrome. If adrenolutin is thus formed but in excess by schizophrenics and if, as Hoffer and Osmond claim, it is psychosis-inducing, these observations may be an important clue to the nature of schizophrenia. However, as far as I know, there are as yet no comparative data on adrenolutin formation from adrenaline between normal subjects and schizophrenics.

In a collaborative study with the Worcester State Hospital and the Departments of Psychiatry and Surgery of the University of Chicago and Billings Hospital, we have studied effects of total adrenalectomy on schizophrenic patients. Eight patients were adrenalectomized by Dr. Charles Huggins and maintained on cortisone or hydrocortisone. Four of these patients had cancer of the prostate or of the breast in addition to their psychoses. This study was undertaken seven years ago in relation to possible abnormal steroid hormone production as a causal factor in schizophrenia, rather than because of any interest we had at that time in the metabolites of adrenaline. We were unable to relieve the psychoses by this procedure. But since the removal of the adrenals also removed most of the source of adrenaline itself, one might expect that if aberrant adrenaline metabolites are involved in maintaining the psychosis the patients would have improved, but such was

not the case. There are other objections that may be raised to the role of adrenaline metabolites in schizophrenia. Thus Elmadjian in our laboratory found that both adrenaline and noradrenaline are excreted in the urine in equal amounts in normal controls and in schizophrenic patients. However, neither these nor other objections that have so far been made have, in my opinion, disposed of this attractive hypothesis which warrants more investigation.

In the course of their studies, Heath and his collaborators (9) concluded that the globulin of schizophrenic patients associated with the copper in their ceruloplasmin might be qualitatively different from that of normal persons. It appeared to bind more copper and in solution to have certain physical properties different from those of the globulin fraction extracted from normal serum. They accordingly isolated this copper-free globulin fraction from the blood of normals and schizophrenic patients and proceeded to inject these preparations into nonpsychotic convict subjects who volunteered as guinea pigs for the experiments. They have thus injected intravenously into the group of volunteers protein fractions from schizophrenics 18 times, and fractions from controls and various placebos on 11 occasions. They have reported that in the cases of the injection of the protein extract from schizophrenics, which they have named taraxein, the volunteers often developed bizarre and psychotic-like behavior beginning a few minutes after injection and lasting for an hour or so. They have shown striking motion pictures of this behavior which is in sharp contrast to persons receiving a similar fraction from normal serum. They have also reported that schizophrenic patients show abnormalities of electrical spiking in the EEG from the septal and rostral hippocampal regions and that monkeys given taraxein display similar spiking which does not occur following intravenous injections of similar protein extracts taken from normal serum. However, Eli Robins has been unable to confirm these reported psychotomimetic effects of taraxein and the control procedures used by Heath *et al.* have been criticized (17).

Studies of psychotic behavior suffer from lack of adequate animal tests and bioassay procedures. A number of tests of psychotomimetic drugs are in use, but none are very satisfactory. Winter and Flataker (23) of the Merck Research Institute have developed a simple behavior test which measures confusion induced by drugs in rats. Rats are trained to climb a rope from a platform near the floor to a platform about 6 feet high containing food. Food-deprived rats learn to do this after a training period and dash up the rope to the food in a few seconds after they are placed on the lower platform. The administration of certain drugs will slow up this well-learned behavior. Thus LSD, a powerful agent that produces transient psychotic experiences in man, will produce confusion and climb-time delay in the trained rat injected with 0.1 to 0.5 mg./kg. of LSD. The climb-time delay builds up to a peak of maximal delay in 30 to 60 minutes and then falls off again to normal preinjection values in another hour. The rat behavior is quantifiable and can be used as a bioassay for LSD. The effects of LSD have been shown to be antagonized by serotonin and by its precursor 5-hydroxytryptophan in this experiment while other drugs may enhance or inhibit the effects of this and of other psychotomimetic agents. Winter and Flataker (22) have reported that 1 cc. of serum from schizophrenic patients injected into rats causes more delay than the corresponding amount of serum from normal controls. Their study consisted of comparing serum samples from 80 psychotics most of whom were schizophrenics, with serum from 47 normal controls and serum from 36 physically ill patients on the climb-time delay of the rats. There was no significant difference in the climb-time delay from serum of normal subjects and physically ill pa-

tients but the climb-time delay averaged approximately 5-fold greater for rats injected with serum from the psychotic patients. We, in our laboratory (unpublished), have studied this same phenomenon and confirmed the effects of LSD and serotonin but have been unable to show consistent differences between serum samples from schizophrenics and normal controls. This is especially confusing since in an initial study involving experiments on the rats with serum from 17 schizophrenics and 10 controls we confirmed Winter's observations. Subsequently, however, using serum samples from many more patients and controls and employing, so far as we know, the same procedure, we have been unable to confirm either Winter's results or our own preliminary findings. Differences in seasonal responsivity of the rats may be a possible basis for this discrepancy and the work is continuing. Winter's group have fractionated serum from schizophrenic and normal subjects and studied the effects of the various fractions on climb-time delay in their trained rats. Results of this study are not yet available. We also are engaged in a study of Cohn fractions from schizophrenics and normals using the Winter rat test. The protein fractionations are being carried out for us by the Protein Foundation. Results of these procedures are still too preliminary to warrant comment at this time.

So far we have reviewed evidence for possible roles of abnormal adrenaline metabolites and also for a protein factor which may play determinative roles in schizophrenia. Quite a different approach has appeared in a recent paper by Mark Altschule (4). He has studied effects of aqueous extracts of acetone dried beef pineal substances on chronic schizophrenic patients. Earlier workers have reported such extracts to produce transient beneficial clinical improvement but refractoriness to the extracts soon developed. Altschule confirmed this and found that daily injections corresponding to 1 gram of the powder in aqueous solution resulted in clinical improvement in eight chronic schizophrenic patients but refractoriness developed in about a week of treatment. Accompanying the clinical improvement there was an elevation in blood glutathione and eosinophils, both of which are known to be low in schizophrenics. Both of these measures fell again with relapse of the improved clinical state accompanying the development of refractoriness to the pineal extract. Altschule then proceeded to remove protein from his extract and obtained an alkaline protein-free solution which when neutralized was injected into the patients. This extract was as effective as had been the original one in producing remission of psychotic symptoms and elevations in levels of glutathione and eosinophils. Repeated injections up to several weeks produced no sign of refractoriness and the improvements lasted for about a week after cessation of the injections; relapse then occurred first in the levels of glutathione and eosinophils with clinical deterioration following later. The protein could be removed from the solution of pineal material by the use of trypsin and centrifugation without depleting potency of the extracts. This suggested to Altschule that enteric-coated, protein-free pineal extract may be taken orally and such preparations are to be tested. It was not possible to continue the injections for longer test periods because not enough pineal material was available. It takes 1 gram of powder for one injection and this requires 15 beef pineals. This is a promising lead and certainly will be explored further. The nature of the active pineal principal is unknown although Altschule suggests that it may be a polypeptide with a molecular weight of about 1000.

Let us now turn to a fourth and still different biochemical approach to schizophrenia, an approach that has stimulated interesting work in recent years and which deals with the possible role of serotonin

(5-hydroxytryptamine) in the brain. Serotonin, a vasoconstrictor, was discovered a decade ago by Irvine Page and his collaborators in their investigations of hypertension. Serotonin is primarily concentrated in intestinal tissue and in blood platelets but is also present in other tissues including the brain. It is normally present in a bound form and is rapidly destroyed by monoamine oxidase when the serotonin is free in the circulation. Woolley and Shaw in 1952 were interested in investigating substances which might act as antimetabolites against the hypertensive action of serotonin and be useful to reduce hypertension. They tested a number of compounds possessing structural similarities to serotonin to observe their *in vitro* effects on smooth muscle made to contract by applications of serotonin. One of the most powerful antimetabolites turned out to be lysergic acid diethylamide (LSD) which since its discovery and synthesis by Hoffman in 1943 has been known to be remarkably effective in minute doses in producing psychotic-like experiences in human subjects when taken by mouth. Investigations of a number of other compounds as antimetabolites to serotonin in relation to smooth muscle contractility turned up other substances possessing indole rings as do both serotonin and LSD, and like LSD, most of these compounds which included medmain, harmine and yohimbine were found when administered to man or animals to produce disturbances of the nervous system and to have unpleasant side effects. They found that the compounds of this group affected the mind, producing unpleasant or bizarre experiences or even out-and-out seizures in animals (24, 25).

Investigations of Vogt and her collaborators using bioassays and those of Udenfriend *et al.* using spectrofluorometric procedures have demonstrated the presence of serotonin in the brain especially in regions of the hypothalamus (see Gaddum (7) for citations and discussion). Noradrenaline has also been found to be present in the brain in these same areas in appreciable amounts. In view of all this, Woolley and Shaw (25) proposed that LSD may exert its psychotomimetic effects by competing for serotonin in the brain as an antimetabolite and thus reduce the quantity of effective serotonin at critical regions of the brain. They also suggested that endogenous psychoses might result from too little brain serotonin. However, they also considered the possibility that too much brain serotonin might lead to a psychosis. Thus they considered that serotonin might be rapidly destroyed by monoamine oxidase and if LSD were to compete for this enzyme for serotonin receptors as an antimetabolite, in the model psychosis the serotonin would be spared and might accumulate in excess at critical loci in the brain.

This hypothesis of Woolley and Shaw (25) has received much criticism. Thus Gaddum and Vogt (see Gaddum (7) for references and discussion) have demonstrated that a violent type of rage response in cats is produced by LSD injected into the lateral ventricle. Serotonin on the other hand has the opposite effect. It produces a catatonic-like stupor. But brom-LSD, which is a potent antimetabolite to serotonin in its effects on smooth muscle has no effect intracisternally in the cats. Cerletti and Rothlin also found that brom-LSD has no psychotomimetic action in man despite its almost equal potency *in vitro* as an antimetabolite to serotonin on smooth muscle of arteries. It appears to pass through blood brain barrier since it causes some sedation. Moreover, a number of antagonists to LSD such as ergometrine and dibenamine antagonize the smooth muscle effects of LSD but have no mental effects at all. On the other hand, Montonari and Tonini have reported that LSD-induced psychotic states are reversed by administered serotonin, but this effect is not specific since it has been established that many substances including reserpine, chlorpromazine,

Frenquel, niacin, and even aspirin may also relieve the LSD-induced psychosis. We have already mentioned that the confusions of rats induced by LSD and measured by their speed of climbing a rope in Winter's experiments are antagonized by serotonin, and Woolley and Shaw (24) have reported that certain LSD-induced bizarre changes in locomotion in mice are overcome by the antagonistic action of serotonin injected into brains of the mice. They have further studied effects of LSD and serotonin on the pulsations of human oligodendroglia cells grown in tissue culture. Serotonin enhances these contractions and LSD antagonizes the serotonin effects. They suggest that the pulsations of these cells may be of importance as stirring mechanisms for extravascular fluid in the brain (24).

Injected serotonin passes the blood brain barrier to only a very small extent. Its systemic administration in large amounts is not detectable in appreciable amounts as increased brain serotonin. That it does get into the brain, however, is indicated by modifications of the brain electrical activity. Marrazzi and his collaborators (15) using cats, and we (19) using rats, have found that both LSD and serotonin, this latter in doses as little as one microgram, together with a number of related compounds, act to inhibit synaptic conduction of the trans-synaptic potential in the optic cortex of these animals when under barbiturate anesthesia. We further have found marked inhibition (induced by doses as small as one microgram) of the electrohypothalamogram and electrocorticogram in rats following injected serotonin. Somewhat larger doses of LSD, adrenaline, noradrenaline, and adrenochrome all have similar effects. But there is no evidence of antagonistic action between any of these drugs, so far as these electrical studies go.

The main pathway of serotonin metabolism has been established by Udenfriend and his collaborators (21). The amino acid tryptophan becomes 5-hydroxytryptophan which is decarboxylated to 5-hydroxy tryptamine and then for the most part is metabolized to 5-hydroxyindole acetic acid. Injected into animals 5-hydroxytryptophan readily passes the blood brain barrier and there is synthesized to serotonin markedly increasing the brain's content of this substance. Thus 60 mg./kg. of 5-hydroxytryptophan injected i.v. into dogs has increased their brain serotonin 10-fold. Animals so treated display behavior not unlike that seen following the administration of LSD. This is characterized in dogs and monkeys by excitement and disturbed psychomotor co-ordination. The serotonin content of brain can also be reduced since vitamin B6 (pyridoxine) is an essential coenzyme for the activation of the enzyme amino acid decarboxylase that forms serotonin from 5-hydroxytryptophan. Udenfriend *et al.* (21) decreased brain serotonin in chicks as much as 60 to 80 per cent by feeding them a pyridoxine-deficient diet. This was accomplished by a number of marked neurologic disturbances but these effects may not be specific for serotonin deficiency since pyridoxine lack in the diet also disturbs the metabolism of adrenaline, noradrenaline and histamine.

The question of the possible role of serotonin in psychoses has had a more direct application from collaborative studies, suggested first by Woolley, with us and with investigators at the Worcester State Hospital (unpublished). Dr. Woolley furnished us with two substances—5-hydroxytryptophan and 1-benzyl-2,5-dimethylserotonin, abbreviated BAS. This latter compound has been shown in clinical studies to act as an antimetabolite to serotonin and to produce some decrease in blood pressure in hypertensive patients. Unlike some of the other antimetabolites to serotonin mentioned earlier, it lacks undesirable mental side effects. The administration of serotonin precursor 5-hydroxytryptophan, while presumably penetrating the blood brain barrier in man as it does in animals and so in-

creasing the serotonin content of the brain, also elevates intestinal serotonin resulting in gastric distress. This limits its use to increase brain serotonin in man. BAS on the other hand penetrates the blood brain barrier little, if at all, and acts as an antimetabolite to prevent the effects of intestinal serotonin. The administration of these compounds together, however, should make it possible to elevate brain serotonin in man without accompanying intestinal distress. Experiments were carried out in which daily doses of these substances were administered in different amounts. For example, schizophrenic patients were given 100 mg. of BAS daily by mouth and after two weeks 5-hydroxytryptophan was administered i.m. in daily doses of 100 mg. In addition two of the patients received iproniazid (Marsilid) in 100 mg. doses daily during the last two weeks of the study. This drug by its inhibition of monoamine oxidase, a serotonin destroying enzyme, should further increase the amount of serotonin in the brain. The results of these experiments were entirely negative. The patients did not show clinical change of any sort. The inferred increase in brain serotonin by this procedure had no detectable effects on behavior, but the amount of brain serotonin increase was of course not measurable and may have been small.

We have described the primary course of the metabolism of serotonin. This appears to be the normal pathway in the formation and destruction of serotonin but a number of other metabolic pathways may be available and might function, were disturbed enzymology to play a role. Thus bufotenine is a dimethylated form of serotonin. It is a 5-hydroxy dimethyltryptamine. This compound has not been found in normal body fluids and has not as yet been adequately investigated in schizophrenics. It does, however, when administered to normal subjects, cause psychotic-like disturbances according to Fabing. It also produces LSD-like effects in monkeys (6). Were it to be formed in strategic loci of the brain in the course of metabolism it might produce endogenous psychoses. Another powerful psychosis inducing agent in man is dimethyltryptamine which is bufotenine minus the hydroxy group. St. Szara (20) has shown this also to be an hallucinogen.

Since many of the substances we have just been considering contain indole rings and amine groups it has been of interest to study the excretion of indoles in normal subjects and schizophrenic patients. We in our laboratory and investigators from other laboratories have presented evidence that there are in fact both qualitative and quantitative differences in indole compounds found by paper chromatography in urine samples from normal persons and schizophrenics (2). Work is now under way in several places to isolate and delineate chemically these different substances in hopes that they may indicate the production of endogenous, psychotomimetic agents. We and others have found that 5-hydroxyindole acetic acid, the principal metabolite of serotonin is excreted in equal amounts by schizophrenics and normal subjects although the day-to-day variability is much greater in the patients. This finding does not however, rule out the possibility of the aberrant intermediate production of metabolites such as bufotenine in the patients. Such substances could be active in very small concentrations in special sites of the brain. Moreover, other pathways of indole production not involving serotonin at all may play a possible role.

We have briefly reviewed some biochemical investigations of schizophrenia currently underway in several laboratories. Many other important contributions have not been considered here for lack of time. There appears to be little connection between studies of proteins such as taraxein, possible aberrant indole metabolites, and effects of pineal extracts on psychotic behavior. It is clear that despite these leads

we are still groping pretty much in the dark. Which if any of these studies will finally contribute to an understanding of the fundamental biochemical lesion or lesions of schizophrenia remains for future work to determine.

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STATISTICAL CONTROL STUDIES IN NEUROLOGY

IX. The Gordon Sign

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In view of the rather meager body of data concerning the incidence of the Gordon sign, two large groups, one of patients and one of healthy people were studied to determine the frequency and significance of this sign.

Gordon (8) described the sign in 1905; he considered it a sign of a motor tract disturbance. In a subsequent paper (9) he emphasized its value as a sign of irritation or early stage of a motor tract lesion. Gordon (10) cited two cases as anatomic proof of value of the reflex; one, verified by autopsy, in which a localized hemorrhagic pachymeningitis was found and the other case, verified by operation, of a localized cerebral trauma. In the technique employed by Gordon the patient sits with the feet on a stool. "The examiner who is always on the outer side of the patient, places the thenar and hypothenar on the inner surface of the tibia, and with the fingers exercises deep pressure on the calf muscles (the pressure must be deep in order to be transmitted to the flexor muscles)." If the reflex is present, extension of the great toe or all the toes will be noted. He called attention to its presence in general paresis (11). It may be associated with exaggerated reflexes but without ankle clonus, Babinski, or Oppenheim signs as demonstrated in 4 cases all with cerebral lesions (10).

The only studies regarding the frequency of occurrence of the Gordon sign were those of Gordon (9) and Elinson (5). Gordon (9) examined a series of 150 normal people and 55 patients with functional nervous disorders; no Gordon sign was obtained. Elinson examined 351 subjects; 236 healthy people; 165 adults and 71 children. No Gordon sign was elicited in the adult group. In the 71 children 5 had Gordon signs; 26 had Babinski signs. Elinson accepted it as a pyramidal tract sign; he found it less frequently than the Babinski and about as often as the Oppenheim. Elinson disagreed with Goldflam's (7) claim that pain is a factor in the elicitation of the Gordon sign. Goldflam stated that the sign is a strong reaction to pain induced during the test. Elinson excluded pain as a significant element since the sign could be demonstrated in patients with anesthesia. Although Goldflam was of the opinion that the Gordon sign could be elicited in normal people, he gave no figures as to the number of people examined or as to the incidence of the sign. Goldflam concluded that the Gordon sign is inconstant in the same disease and is of no diagnostic value except for its appearance prior to the hyperesthesia of meningeal disorders. Oppenheim (18) stated that the Gordon sign was a modification of the Babinski sign; its elicitation being obtained by stimulation of another zone. Dejerine (3) held a similar view. Auerbach (2) indicated that it is present where Babinski, Rossolimo, Mendel-Bechterew signs or clonus are detectable. It is similar to the Oppenheim sign. It is a subcortical sign. Walshe (22) wrote that the Gordon sign is no more than "the extensor plantar response elicited from a different part of its receptive field." Alpers (1) stated "it appears in corticospinal disease." Nielsen (17) Wechsler (23) Monrad-Krohn, (16) Purves-Stewart, (20) Grinker and Bucy (12) all considered the Gordon Sign as a pyramidal tract sign.

[1] From the Neuropsychiatric Service of the Morrisania City Hospital, New York.

TABLE 1

Incidence of Gordon sign in 2500 cases with other evidences of lesions in the nervous system

Age	Sex	Race	Unilat.	Bilat.	Diagnosis	Other evidences of lesions in the nervous system.
yr.						
26	M	W	R		Bronchiectasis.	Right Rossolimo
59	F	W	L		Bleeding peptic ulcer.	Left Oppenheim; deep reflexes greater on left side; cutaneous abdominals absent.
64	F	W	R		Acute cholecystitis.	Right Oppenheim; bilateral Babinski; cutaneous abdominals absent.
54	M	W		+	Arteriosclerotic heart disease.	Bilateral Oppenheim and Schaefer.
36	F	N	R		Cervical stenosis.	Right Schaefer; defective plantar responses.
58	F	W	R		Cancer of uterus.	Right Oppenheim; bilateral Babinski; left cutaneous abdominals absent.
77	M	W		+	Hypertensive heart disease.	Position and vibration impaired in lowers; right cutaneous abdominals absent.
45	M	W	L		Acute glomerular nephritis.	Left Oppenheim; defective left plantar response.
6	F	W	L		Lobar pneumonia.	Left Oppenheim.
43	F	W	R		Peritonsillar abscess.	Right Oppenheim.
21	F	W	R		Incomplete abortion.	Right Schaefer; right patellar greater than left.
66	F	W	L		Cancer of stomach.	Left Schaefer.
48	M	W	L		Rheumatic heart disease.	Left Oppenheim; right Babinski.
64	F	W	R		Insulin shock.	Right Oppenheim.
41	M	W		+	Peptic ulcer.	Bilateral Oppenheim.
69	M	W	R		Luetic heart disease.	Left Babinski.
51	M	W	L		Diabetes mellitus.	Left Oppenheim; vibration diminished in lowers.
40	F	W	L		Chronic salpingitis.	Bilateral Babinski; left patellar hyperactive; right ankle jerk absent.
67	M	W		+	Cancer of mouth.	Bilateral Oppenheim and Chaddock; left Babinski.
68	M	W	L		Coronary sclerosis.	Left Oppenheim.
69	F	W		+	Cancer of stomach.	Bilateral Oppenheim and Hoffmann; right Babinski; right cutaneous abdominals absent.
70	F	W	L		Hypertensive heart disease.	Right Babinski; left patellar greater than right.
20	F	W		+	Acute salpingitis.	Bilateral Oppenheim and Babinski; cutaneous abdominals absent.

TABLE 2

Incidence of Gordon sign in 2500 cases without other evidences of nervous system disease

Age	Sex	Race	Unilat.	Bilat.	Diagnosis
yr.					
14	M	W	R		Bronchopneumonia.
69	F	W	R		Cancer of uterus.
51	M	W	L		Hypertensive heart disease.
47	F	W	L		Pelvic abscess.
69	F	W	L		Hypertensive heart disease.
59	M	Japanese	L		Peptic ulcer.
33	M	W	L		Rheumatoid arthritis.
75	F	N	L		Intestinal obstruction.
67	F	W	L		Diabetes mellitus.
69	M	W	R		Cancer of colon.

Price (19) described a patient with a spinal injury in which the Gordon sign appeared 3 days before the Babinski reflex and in which it was the last sign to disappear. According to Fulton (6) the Gordon sign is similar to the Babinski reflex, both being in the category of withdrawal responses to nociceptive stimuli. DeJong (4) included the Gordon, Oppenheim, Schaefer and Chaddock signs as pyramidal tract signs and wrote, "it is occasionally possible to elicit one or more of these when the Babinski sign cannot be obtained."

MATERIALS AND METHODS

Two groups of people were studied.

Group 1 was composed of 2500 patients with non-neurologic diseases admitted to the surgical, medical and obstetric wards of the Morrisania City Hospital. There were 1695 females and 805 males. The ratio is greater than the ratio of 100.6 females to 100 males in the Bronx, according to the census of 1930. The greater number of females is probably due to the large gynecologic and obstetric division in this hospital. Negroes comprise 1.02 per cent of the population of the county; of the series of 2500 hospital patients, Negroes constituted 18.6 per cent of those examined. The greater number of Negroes in the series is most likely due to economic conditions and the fact that the hospital is a city institution.

Group 2 was composed of 706 inductees, all male, between the ages of 21 and 35. In the present investigation the technique employed in the test was that of Gordon, except that the patient was lying in bed, and not sitting in a chair. The feet were slightly rotated laterally, since in this position complete relaxation of the muscles of the leg can be obtained. Dorsiflexion of the big toe was necessary for the reaction of be considered positive.

RESULTS OF STUDY

Group 1. Of the 2500 non-neurologic hospital admissions, 33 had Gordon signs, an incidence of 1.32 per cent. Tables 1 and 2 list the cases of the Gordon sign with other signs of lesions within the nervous system and without other signs of lesions within the nervous system respectively. Thus from Table 1, of the 23 patients with Gordon signs and with other evidences of nervous system disease, 6 had bilateral signs; of those with unilateral signs, the Gordon sign was present on the right side in 8 and on the left side in 9. From Table 2, of the 10 patients with Gordon signs and without other evidences of nervous system disease, the sign was present only unilaterally, on the right side in 3 and on the left side in 7. The incidence of the Gordon sign rises from 0.49 per cent in the 20 to 39 year age group to 4.30 per cent in the 60 year and older age group. Increase in the frequency of the Babinski (21), Hoffmann (13), and Oppenheim (14) signs with age were reported in previous studies; however an increase with age was not observed with the Rossolimo sign (15). Chi square test, as seen in Table 3, indicates a statistical significance between increase in the incidence of the Gordon sign with rise in age. The Gordon sign was present in 0.68 per cent of the Negroes, as compared to 1.40 per cent of the white patients. The difference may be partially explained by the greater number of Negroes in the younger groups. Of the patients in Group 1 with the Gordon signs, 69.8 per cent had other signs of lesions within the nervous system. Thus the presence of a Gordon sign is in favor of nervous system disease; it is a pyramidal tract sign.

TABLE 3

Incidence of the Gordon sign with age

Age group, yr.	0–39	40–59	60 and over
Total no. in group	1470	705	325
No. with Gordon sign	7	12	14

$\chi^2 = 32.55$, $p < .001$

Group 2. In the inductee group, the Gordon sign was not present in any of the 706 men. There were 4 Gordon signs in the 781

patients between the ages of 21 and 35 of Group 1 with an incidence of 0.51 per cent.

SUMMARY

1. The incidence of the Gordon sign was investigated in two control groups: Group 1, consisting of 2500 non-neurologic admissions to a general hospital, and Group 2, of 706 inductees between the ages of 21 and 35.

2. The incidence of this sign was 1.32 per cent in the 2500 non-neurologic admissions of Group 1. It was not present in any of the inductees of Group 2. It was present in 0.51 per cent of the patients between the ages of 21 and 35 of Group 1.

3. The Gordon sign increases in frequency with rise in age.

4. Race is not a factor.

5. Since it occurred with other signs of lesions within the nervous system in 69.8 per cent of the 33 patients who had the sign in the non-neurologic admissions, the presence of the Gordon sign is in favor of disease of the nervous system, the involvement being either interference with the function or actual lesion of the pyramidal tract.

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It should be the function of a scientific journal to reserve space from time to time for the presentation of original theoretical formulations. To be worthwhile a purely theoretical development should be creative at a level of considerable sophistication. It should introduce concepts that can be put to experimental test; it should stimulate the curiosity of other investigators. William Greene's inquiry into the physiologic interaction of mother and child is such a contribution. This is a fresh and original exploration that bears on a number of fields, and does not fit readily into any fixed discipline. Its impact will surely be controversial. We should be much interested in the appraisals of our readers and their reactions.

The Editors

EARLY OBJECT RELATIONS, SOMATIC, AFFECTIVE, AND PERSONAL

An Inquiry into the Physiology of the Mother-Child Unit

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I. Consideration of Retrospective Observation

Psychoanalytic technique and theory, as developed during the past six decades from Freud's original formulations have provided the most useful bases for understanding both intrapsychic and interpersonal

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processes. Even so, traditional psychoanalytic techniques of retrospective observation and reconstruction present limitations in comprehending very early phases of human development and there is increasing agreement that further progress in understanding early infantile development must be made through direct observation and consideration of the experience of the infant himself (66, 90).

Current psychoanalytic theory suggests that the traditional Freudian duality of early psychic structure with a primary Id and developing Ego is difficult to demarcate at earlier and earlier stages of development and is now conceptualized as a duality developing out of a single undifferentiated state (56). The term, undifferentiated, is variously used and understood. As originally formulated by Hartmann (55) this implies a state in which the Ego is not differentiated from the Id and the Id is not differentiated as such and does not exist any more than does the Ego. The term undifferentiated state is at times used with the inference of a lack of integration, no regulation, and general chaos. This inference is understandable since in psychoanalytic theory the Ego is the key integrating and regulating structure of the mental apparatus and no Ego means no integration, no regulation. However, Hartmann with his extensive, but astute and critical, conceptualization points out there must be more primary biologic autonomous attributes for control and adjustment.

Similarly, current psychoanalytic theory suggests that the traditional Freudian duality of libido and aggression, when observed and conceived at earlier and earlier stages of infant development, is not so discernible as a duality; but may be fused as one instinct or an undifferentiated instinct (94). This assumption of an undifferentiated monistic instinctual concept appears to be based partly on the inability to trace evidence of the above duality with psychoanalytic constructs and techniques during early infantile stages.

Another duality in traditional psychoanalytic theory has been the Ego and reality or Ego and environment, perhaps Ego and object. This duality has currently metamorphosed into self and Ego and object (56). These psychoanalytic constructs constitute the most useful bases for understanding object relationships. However, throughout the evolution of psychoanalytic theory, the assumption has persisted that, while there develops a differentiation between Ego and object or self and object, no such duality exists in early infantile or neonate experience. Rather it is assumed that there is an undifferentiated phase in which to the neonate the so called environment, or objects, or part objects are part of the self.

It appears that here may be an impasse something like that of an investigator who spends years studying and defining the visual apparatus, its perceptive, differentiating, integrating, and synthetic functions, not only at one stage of development but at all stages, and who then discovers that there is a stage of development when visual function does not transpire. He might conclude that prior to this point the organism must be a scattered, unregulated, chaotic mess, with no kind of perceptive function. Perhaps he would conclude that there is a stage in the development of the organism when the visual apparatus, so well understood and explained by himself, is neither developed or needed. He might then reexamine his observation, description and interpretation of the visual apparatus and further determine their usefulness. Again he might decide to study other systems, the endocrine glands, the vascular system, or the gastrointestinal tract, but approached as "inner eyes" to be appraised with the techniques, language, and constructs of optical physics.

It is chiefly to the premise that there are no objects to the very young or newborn

infant that this inquiry is directed. It is my premise that there is perception of a kind of object by the newborn and in addition what perhaps may be termed an object or objects during prenatal development. For the purposes of understanding the processes to be examined in this paper an object will be considered in terms of that which can be "perceived" by the developing organism *via* some biochemical or physiologic level of organization and such processes may be viewed as object relationships. Questions of when or how such objects or object relationships acquire affective components and/or psychic representations will not be considered even though these qualities are of significance in object relationships and constitute the main elements considered in psychoanalytic concepts. As pointed out by Spitz the stage of the developing human organism up to three months appears to be more biologically than psychologically understandable (90). Psychoanalysis has concerned itself mainly with the psychologic aspects of object relationships. I will be more concerned with the biologic aspects.

Psychoanalytic theories have been developed by retrospective synthesis from reconstructive data observed in adults and from data of direct observation of children and infants. These bases of investigation have led to the several undifferentiated aspects mentioned, including the premise that there is no differentiation of an environment or object to the newborn. Perhaps this later assumption stems mainly from the admonition of Freud that "We must not forget that during its intra-uterine life the mother was not an object for the fetus and that at that time there were no objects at all as far as it was concerned" (40). This may be the only inference possible from retrospective observation. When one looks a mile back down the railroad tracks the tracks obviously fuse and there is no differentiation. But is one walks back a mile and looks more closely, this may not prove to be the case.

II. THE UMBILICAL OR VASCULAR STAGE OF DEVELOPMENT

Study of a group of patients with leukemia or lymphoma has indicated that these patients develop the manifest disease in a setting of emotional distress, chiefly depression incident to the loss of some key object or goal for the individual (51, 52). From these findings and continued study of these patients, men, women, children and their mothers, and one case of congenital leukemia, I was faced with the question of how to comprehend, much less explain, the occurrence of disease at the reticuloendothelial or vascular level of organization in association with and apparently precipitated by a disturbance in interpersonal relations, usually the loss of the mother or a mother figure. In solution of this dilemma I jumped to the premise that during much of fetal life the vascular system of the fetus is "outside" to the fetus; that this is the environment to the fetus comparable perhaps to the gastrointestinal tract at a later, postnatal period of development of the organism (53, 54). From these premises I suggested considering an umbilical stage of development in comprehending certain psychosomatic phenomena, comparable to the traditional oral, anal, phallic stages which are the traditional sets for perception and interpretation of many types of psychophysiologic disease. I also suggested that the boundary of interaction of each level of organization constitutes the environment of that level of organization and each such boundary of interaction has been at a stage of growth, the external environment to the then whole organism. This means that a boundary, an environment, and a level of organization may be morphologically the same but varying in function with time and frame of reference. As a boundary becomes an environment and in turn becomes a level

of organization, growth and development proceed.

THE VASCULAR ENVIRONMENT

I wish now to take up again this train of thought, to elucidate it more fully, and then to use this as a basis for prospective, not retrospective, conceptualization regarding the environmental or object world of the developing, growing, fetal organism. This will involve speculation and pondering, not only what it is like to be a baby which has been done at length from retrospective material from adults and from observation of babies, but even what it may be like to be an even younger baby, a fetus. While any provable idea of this may be impossible of attainment, from certain known facts, processes, and events, inferences of what it is like to be a fetus may be arrived at with a degree of accuracy which will be fruitful.

First it is considered that the environment during most of fetal life is the fetal vascular system together with the umbilical and fetal-maternal placental system. Variations in the attributes of this system, constituting actually two boundaries, and two environments provide both the nutritive and eliminative needs of the organism. We will consider only oxygen, water, carbon dioxide and glucose to avoid questions of what does and does not pass the placental barrier. I propose that these compounds or their concentrations, or combinations of their concentrations are a kind of object for the developing organism at one stage of development. A precendent for this application of the term "object" is Kubie's use of the term "chemical object" in his evaluation of the concept of instincts although he does not consider prenatal stages (67). The fetal organism must relate in various interreactions[2] with these kinds of objects. Work on the part of the organism to maintain satisfactory relations with these kinds of objects is necessary. Fetal needs are not inevitably satisfied even though they may be

[2] The term interreaction is here used to describe a kind of relationship within and of organisms. It is a term used in place of the traditional term interaction which may connote either "between" and "in between" or "mutually" and "reciprocally" (21). However, interaction connoting a mutual, reciprocal, open system relation has been employed as a frame of reference in observation, thinking and conceptualization for years by some investigators (10, 57). This approach to the study of biologic systems is closely akin or the same as the currently popular transactional approach. However, I refrain from using the term transaction as much as interaction since transaction also is very nebulously used in current thinking and writing, particularly in relation to problems of psychosomatic phenomena. Transaction may be appropriately used in the second sense of interaction noted above. However, it is too often employed as a means to relate phenomena as though use of this term or perspective makes phenomena relate, without in any way indicating the quantitative or qualitative aspects of the relationship. Thus Dewey and Bentley (22) state in reference to transaction, "Our assertion is the right to see in union what it becomes important to see in union; together with the right to see in separation what it is important to see in separation—each in its own time and place; and it is this right, when we judge that we require it for our own needs, for which we find strong support in the recent history of physics." This sounds like a highly self actional approach. Our own needs may require that we judge what is or will become important to see in union or in separation.

In some investigative parlance the multicausality of a decade ago inferring that things are rough all over, has been replaced by transaction inferring that everything is really just fine and all goes together nicely. At times it almost seems that transaction is invested with the significance of a vital force. For a while longer transaction should be left with the physicists.

Interreaction connotes a biologic situation where there is a definable point of reference A from which there is a definable reaction a′ and a definable point of reference B from which there is a reaction b′. The determinants of reaction a′ at A may or may not be apparent or demonstrable. Similarly the determinants of the reaction b′ at B may or may not be apparent or demonstrable. This means that observed situation A is considered an open system and observed situation B is considered an open system. Now if A and B are viewed together, a′ and b′ must be viewed together. But a′ may not be an appreciable determinant of b′ or *vice versa*. Only if it can be assumed or perferably demonstrated that there is a statistically significant relation between a′ and b′ do we label Aa′ b′B an interreaction. This perhaps too rigid definition is made with the awareness that interreactions may be of widely different orders varying from very close to far distant.

relatively simply fulfilled, and even though the mother's homeostatic mechanisms provide a fairly stable environment of the type needed. However, the amount of oxygen, water and glucose obtained by the fetus during any given time and the amount of carbon dioxide expelled is not entirely determined by the mother and passive physiochemical diffusion processes. Rather variations in the amount of oxygen acquired and the amount of carbon dioxide expelled, both in the fetal vascular system and at the placental barrier, in any unit of time is determined by the rate of fetal blood flow. As shown recently by Reynolds the main factor determining fetal placental blood flow is the fetal cardiac output (81). As he says, "What more effective arrangement could Nature devise than that the fetal heart provide for its own welfare."

This perspective is contrary to the general assumption that *via* the placenta the mother takes care of all the fetal needs, without effort on the part of the fetus. The same general assumption usually has been made that the organism much later in "physiologic time" (75) has all of its nutritional needs provided without effort or control on the part of the newborn baby. However, the rate or amount of milk consumed in a given time is determined to an appreciable degree by the baby. This is so whether the baby is on so called demand or scheduled feeding. Balint stressed nearly 20 years ago that contrary to common parlance, the child is not suckled, it sucks actively (8). As stated by Escalona (30)[3] in her paper replete with perceptive inferences made from observation of many baby-mother[4] relationships:

"Active cooperation is required of him so that a smooth feeding constitutes the earliest mutual (instead of one sided) adaptation between mother and infant. You can put him to breast but you can't make him swallow. This is an interesting supplement to the phychoanalytic idea that feeding is the ultimate in receiving and absorbing without having to pay for it, so to speak . . . I do not consider it impossible that the importance which breast feeding can have in the developing mother-child relationship is anchored in the fact that breast feeding requires mutual interaction of a delicate kind, mediated by bodily processes in both mother and child."

Escalona's last statement with reference to breast feeding is important. I would in addition ascribe these attributes to the vascular relationship; that this too constitutes an interaction or mutual interaction of a delicate kind mediated by bodily processes in both fetus and mother. One of the theses to be developed in this paper is that breast feeding is *not* the earliest mutual adaptation between child and mother.

This view of the fetal-maternal rela-

[3] Throughout this paper I shall repeatedly rely on this significant contribution by Escalona. Her contribution is significant because she presents a "conglomeration of impressions, thoughts and fantasies" derived from many hours of observing babies and their mothers and from talking with their mothers. In return I would hope that some of the material, thoughts and fantasies presented here may make her many perceptive inferences more explainable and less conjectural.

[4] I here use the term baby-mother relationship in contrast to the usual term mother-child or mother-baby relationship. Many studies, retrospective and direct, of what it is like to be a baby indicate the necessity of examining the baby-mother relationship as a mutual relationship. However, even though we say this is our perspective, this mutual, reciprocal, hyphenated expression in relation to observation of the neonate usually comes out as mother-child or perhaps mother-baby. I point out that the neonate is a baby not a child. My main point is that this relationship is never expressed as baby-mother or child-mother even though we say we are attempting to surmise what it is like to be a baby. This does not seem or sound right. Even more strange may be what I am attempting to examine here, namely the fetus-mother relationship. I became aware of the "direction" of such relationship terms some years ago in considering the doctor-patient relationship. We say this is a mutual, reciprocal affair but the expression patient-doctor relationship does not sound right. It would seem that for most of us the mother and the doctor have to come first.

tionship as mutual was expressed more numerically by Barcroft with respect to the fetal lamb when he said, "On the 20th day, the mother in effect says to each fetus, 'Here is 2 cc. of blood a minute or 0.4 cc. of oxygen from now till you are born; take it or leave it.' " (12).

As previously proposed then, I suggest that the environment to the fetus during the later months of fetal development is the fetal vascular umbilical system. It is *via* this environment, relatively stable and suitable, that the satisfaction of whatever is hunger, in the sense of food hunger and oxygen hunger at that stage, and the elimination of metabolic products such as carbon dioxide, and the response to noxious agents such as toxins or infectious agents, must transpire. All this I assume to take its course with some direction on the part of the fetus. This concept has proved useful in comprehending, even though not explaining, the apparent occurrence of leukemia in a setting of separation and depression. This for me replaced the traditional premise that the fetus experiences an environment which is all giving, quiet, dark, cozy, stimulus free, a Nirvana devoid of objects, good or bad, and free from toil.

Even so I had continued to assume that this traditional picture applied to the apparent surface boundary of the fetus and this is what is usually viewed as the environment of the fetus since this is where the environment, the outside world, is in the child and the adult. These conjectures get into problems of "inside" and "outside" which is so confusing in problems both of psychogenesis and embryogenesis, and I became involved in this ambiguity in my previous paper. I would now prefer, for purposes of simplification and perhaps increased accuracy, to consider these matters as depicted in Figure 1. This represents simply the general fetal configuration with a surface S and a simplified vascular system V beginning and ending via the umbilical vessels in the placenta. Another reference is point A, a polar orientation, labeled the self *of* or *to* the fetus, borrowing perhaps irresponsibly Hartmann's (55) term. I consider that even for the morula or blastomere there is some orientation with the connotation of self. But here our base for prospective consideration is much later in ontogenetic development. To avoid matters of "inside" and "outside," I then designate for the fetus point A as *here*, any point V as *there* and any point S as *over there*. This may help to avoid or postpone the quandary and the wrangle as to what is "inside" and "outside" *of* and *to* the fetus, the mother, the observer, the author and also the reader. We will now be attempting to consider and imagine an environment from the point of view of the fetus. Whatever this may be it is not an environment in any traditional sense of the environment as outside world. This perspective may well deal too simply in a peripheral dimension with reference to point A. We do not conceptualize in terms of centrifugal and centripetal, but only with more or less centrifugal. Like inside and outside, centrifugal and centripetal may be a function of the observer. Perhaps most important, there is no room here for the concept of primary narcissism but only more or less narcissistic if one is so inclined. The validity of the hypothesis and cushion of primary narcissism has been most adequately disposed of years ago by Balint (8) where he points out the negative, objectless, nonviable attributes which this concept presupposes and requires.

THE SURFACE BOUNDARY

Now to consider the question of what is the perception, if any, at the surface boundary to the fetus, and in particular is this the consistent, quiet, stimulus free boundary usually assumed. I suggest not. Rather I assume that the surface boundary is exposed to the perpetual, recurrent vibrations, pressures, sounds provided by the mother's vascular pulses, emanating chiefly from the uterine blood vessels, the aorta and perhaps

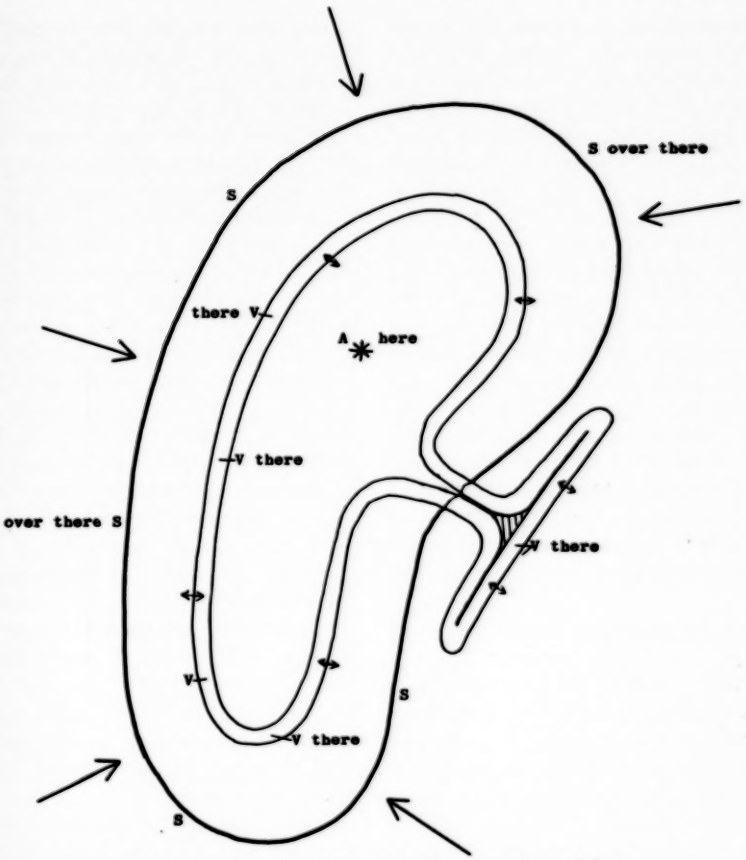

FIG. 1. Vascular environment and surface boundary of fetus.

other abdominal blood vessels. Second, I assume that the surface boundary is exposed to rhythmic pressures incident to the mother's respiratory movements and to a less constant degree, incident to the mother's walking. More conjectural is the suggestion that the surface boundary may be exposed to vibrations, perhaps considered as sounds, occurring during vocal behavior including talking and singing on the part of the mother.

What is the basis for assuming that the fetal surface may be exposed, whether or not there is perception, to such vibrations? Long before the development of some of the more modern instruments for augmenting clinical and research observation, such as the stethoscope, it was known that the chest and abdomen are filled with rhythmic noises. Experience with these by direct auscultation, by the perceptive observer, could impart considerable diagnostic and predictive information.

Assuming that there are such pressures, sounds, and vibrations within the abdominal cavity, this does not mean that they are transmitted to the fetal surface. It would be assumed that they are not transmitted in view of the usual premise that the fetus is shielded from a variety of "external" stimuli by the water cushion of amniotic fluid. However, this water barrier may

dampen some kinds of sounds and vibrations while facilitating others. The fact that the obstetrician can hear the fetal heart beat, albeit with a stethoscope, through the fetal body surface, the amniotic water barrier, the uterine wall, and the abdominal wall of the mother strongly suggests that the relatively loud sounds, incident to the maternal uterine or aortic pulsations are transmitted to the fetal surface. Expecting that this premise may be questioned for a variety of reasons, I would point out that it has been readily considered that sounds, originating much more peripherally and beyond the mother's abdominal wall, induced by patting, buzzers, clapping, bells, applause, music, or washing machines, are associated with movements on the part of the fetus; that these more peripheral and shielded sounds are assumed to pass to the fetus with stimulation and response (88, 89).

I suggest the possibility that the maternal vascular pulsations may provide a rhythmic noise barrier protecting the fetus from these isolated extraneous stimuli during antenatal life. Moreover this proposal of perpetual, rhythmic, stimuli may be an important consideration in interpretation of all operative studies of fetuses. This may bring in another artifact in experimental procedure making debatable the validity of interpretation and extrapolation of stimulus and response observations on delivered fetuses to the natural intrauterine fetal state. This may be another factor to control in addition to those repeatedly emphasized by Windle (99), namely oxygen saturation and temperature of the fetus.[5]

Now even though the premise is valid that there are vibrations, noises, pressures within the mother's abdomen and even though it can be construed that these are transmitted to the fetal surface, this does not mean that these vibrations are perceived over any appreciable period of time, if at all, prenatally. However, it seems unlikely that before birth the fetus would not perceive vibrations or pressures of the intensity and quality, which we here suppose to exist in the intrauterine state, in view of the surface stimuli which it apparently perceives with response shortly after birth. In addition perception of a variety of skin stimuli by premature babies (23, 58) indicates the likelihood that the maternal vascular pulses may well be perceived by the fetus for some time before birth even though there may not be perception of a single pulsation but only of a variation in a repetitive stimulus.

Further substantiation of this assumption is given by the study of tactile stimulation and response in early and late fetal life by Hooker, (61) Windle, (99) and others. While the sequence of development of sensory or motor activity in the fetus is of great importance, as is the sequence of types and localities of perception, such questions are not germane to the theses being considered in this paper. These matters have been extensively summarized by Carmichael (18). This whole problem of fetal stimulation and response has been lucidly and critically considered by Greenacre (49). She views the fetal experience largely as the prodrome for her main focus of interest,

[5] Windle (100) points out, "The relative quiesence of the normal fetus in utero is somewhat surprising when one considers all the activities of which the growing specimen is capable when removed from the uterus. The reason seems to be at least twofold: lack of adequate stimulation and high thresholds in the fetal central nervous system. The fetus is adequately nourished and warmed in a medium lacking practically all the stimulating influences of the environment with which it will have to cope later on. No significant excitation of the external receptors occurs." I am suggesting that there is a kind of repetitive stimulation of some types of external receptors of the fetus. Windle's point then may be like saying the relative quiescence of a normal sleeping baby rocking in a cradle is surprising when one considers all the activities of which the growing baby is capable and usually manifests on removal from the rocking cradle. The quiescence of the baby may be due to both a lack of some kinds of extraneous stimuli and the presence of a certain kind of familiar rhythmic stimulation.

the significance of the birth process itself. Greenacre's main interest in fetal experience centers around the changing pattern of sensori-motor organization. In relation to this she infers some import in pressure stimuli on the fetus incident to the mother's change in position or motor activity.

The only paper which has come to my attention suggesting a role of maternal vascular pulsations as stimuli is an interesting paper by Lourie on infant and childhood rhythmic behavior (70). In this report he considers regression to a uterine state and notes the rhythmic movement of the pregnant uterus incident perhaps to aortic pulsation. Other than this I am aware of no consideration of a fetal surface exposed to the kinds of stimuli suggested here, in spite of the study and interest in fetal behavior both by embryologists and psychologists. Lack of apparent response does not necessarily indicate lack of perception of the stimuli proposed. These stimuli would be recurrent fairly regular in rate and intensity and there may operate the phenomenon of adaptation, "failure in the exciting effect of a constant stimulus" (1). A change in rate or intensity of these repetitive stimuli may be what evokes a response rather than a single pulse beat or pressure or noise.

This is the first hypothesis which I wish to propose in this paper. Namely that during fetal life the developing organism is exposed to and perceives various rhythmic vibrations incident to maternal physiologic processes, chiefly the mother's vascular pulsations and respiratory movements. This may mean that the developing fetal organism becomes increasingly aware of being surrounded by a boundary from which repetitive vibratory stimuli eminate. This may be considered a kind of object during later fetal growth in the sense that awareness of what may be called an object in any system or at any level of organization presupposes some perception of its presence or absence. If it is permissible to assume that the maternal physiologic activities afford a kind of object at the fetal surface during prenatal development, this means assuming that there is a second kind of object perceived by the fetus in addition to those already described for the vascular environment. Further, if this is tenable, I would assume that these kinds of objects are very different to the fetus considering the great difference in the quality of object at the two sites, and also the difference in mode of perception, the one being biochemical and the other neural. There are further differences. The relation between fetus and mother at the vascular boundary is biochemical on both sides. The relation at the surface is *vascular* or *motor* on the part of the mother but *neural* on the part of the fetus. Perhaps the major difference is the fact that the relation at the vascular environment is an interreaction, involving mutual participation on the part of the mother and of the fetus. On the other hand the relation at the surface boundary is a very low order interreaction and may not be an interreaction at all according to our definition. The character of the relation at the surface is not mutual but involves a reaction manifested by the mother, her physiologic vibrations, and only the reception of a perception on the part of the fetus. While some reaction, such as a hormonal response, on the part of the fetus may conceiviably, vary indirectly and slowly effect the mother's physiologic activities, any significant, perpetual effective means is not apparent to me. This supposes that the quality of the relation between fetus and mother at the fetal surface is different and may be unique compared to the quality of both the relationship at the vascular environment of the fetus and the later mutual relationships which have been demonstrated for a number of modes of baby-mother relationship postnatally. Whereas the fetal-maternal relationship is mutual and interreacting, both at the vascular environment and postnatally, it is predominately, if not exclusively, a mother to fetus

relationship that we are considering at the fetal surface. I am struck by the parallel between the differences that I am trying to describe here, and the difference that Escalona (31) ascribes to communication and contagion as follow:

"Mothers, and all other sensible people, know that feelings, purposes, intentions are communicated to and by babies long before speech or specific gesture play a role. How something is transmitted from the mother to the baby, and vice versa has been subject to much speculation, to which I shall add just a little. In discussing instances of social interaction, and the possible role they play in stabilizing and coloring the baby's world, it may be useful to distinguish between two kinds of transmission between the participants. The one I shall call contagion the other communication. Both may be one sided, so that one participant receives, for instance, a feeling of reassurance but the other does not. Or they may be mutual so that something flows from mother to baby and back again. The difference is something like that between listening to the radio and talking on the telephone."

CHARACTERISTICS OF THE MATERNAL PHYSIOLOGIC ACTIVITIES AS AN OBJECT

I have proposed that the vibrations, pulsations, pressures incident to the mother's physiologic activities, chiefly vascular and pulmonary, represent a kind of object, during the later stages of fetal experience. If this premise is valid, then it is pertinent to note certain characteristics of this type of object, an object which is repetitively perceived. However, this object is not a perception which can be realized by the fetus, in the sense that some reaction on the part of the fetus will modify, or make appear or disappear this kind of object. However, the persistent, consistent, repetitive quality of the object makes realization in a sense unnecessary. The object in the sense of a single vibration, pressure, or sound incident to a single vascular systole recurs with a high degree of consistency and one might say confidence. The recurrence in any brief unit of time is consistent, for while the maternal vascular pulse may range from 50 to 120 beats per minute, any such change does not occur abruptly, but only in a gradual fashion. This may be considered as a perception which is present, disappears and reappears perpetually without requiring any effort on the part of the organism. In a sense this has the attributes of the proverbial ideal object. I assume that this is an object in that the fetus has awareness of it and an awareness of it as not part of itself, as *over there* compared to *there* or *there* compared to *here*. However, in some attributes this is not an object in that it is not realizable by the fetus, and it is not an object in constituting a pole in an interreaction. Perhaps it should only be described as an ideal quality of a perception.

CHARACTERISTICS OF THE MATERNAL PHYSIOLOGIC ACTIVITIES AS A CHANGING OBJECT RELATION

What I am postulating as the surface perception to the fetus may be represented in its variety as another simple diagram, Figure 2. Here the mother's various physiologic rhythms mentioned are depicted from bottom to top in terms of increasing frequency of rates which means increasing rate of reappearance or reperception of what I term the object at this surface. While walking, and possible vocal sounds are depicted, we will be mainly concerned with vascular and respiratory rhythms. I assume that there would be a usual range of rates. This range is approximated in the area demarcated by the lines D and S. It is assumed that there are rates of recurrence at times faster and at times slower than the ranges included within DS. This diagram shows pictorially that while there may be appreciable difference between recurrence rates at the top and bottom of the diagram, there is very little difference in any two adjacent frequencies depicted. I

intend in another context, in relation to separation, to consider the time-space problem indicated in this diagram, now only pointing out that while awareness of time may be learned through awareness of distance, time, as rate of recurrence of a perception, and distance have an equivalence.

Freud has said, "We have no way of conveying knowledge of a complicated set of simultaneous processes except by describing them successively; and thus it happens that all our accounts err in the first instance in the direction of one sided simplification and must wait till they can be supplemented, reconstructed and set to right" (42). With this I agree. However, the hazards of over-simplification and only close approximation perhaps may be compensated for by insight gained from attempting to consider complicated processes simultaneously. Eventually, it may prove profitable to look for possible correlations between changes at the vascular environment of the fetus and variations in the perception at the fetal surface provided by alterations in the maternal physiologic activities. Even so, at the present time neither the placental exchanges nor their variations with the mother's cardiovascular adjustments are clearly enough elucidated. Such data may become available as techniques of examining uterine, placental, and fetal vascular physiology *in situ* develop further.

Although it is easy to speculate at length on these matters, assuming that maternal pulsations and respiration afford a kind of object at the fetal surface, I wish only to point out a few further considerations at this time. If these premises are valid, it seems likely that there is a great variety of possible ranges of rates and intensities of the perceptions at the fetal surface suggesting that even *in utero* each baby-mother interreaction may be a highly individual affair. The DS location and range may be high or low depending on variations in these levels and ranges in different mothers. This suggests one perspective in

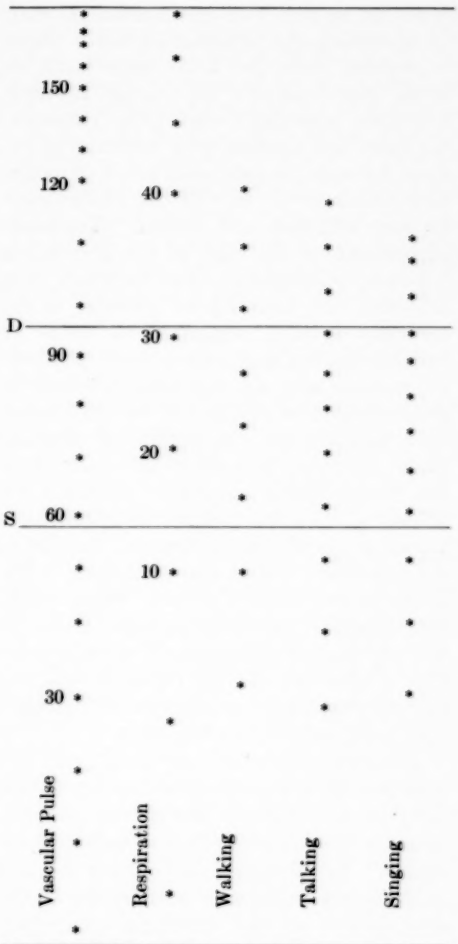

FIG. 2. Variations in rates of maternal physiologic activities.

accounting for the great diversity of reactivity generally and locally in neonates (43–45, 86, 87). In particular I mention the variability in the congenital activity pattern of neonates demonstrated by Fries (43). In her studies one stimulus consisted of vibration or noise of a dropped weight which I presume may afford a diffuse, not localized stimulus and secondly a stimulus involving presentation, removal and resto-

ration of an object of gratification. It may be stretching the imagination but I think it possible that the fetus may learn to "read" the mother's physiologic rhythms to borrow Escalona's term (32). However, the rates and intensities of vascular or respiratory activity compared to motor modes of behavior on the part of the mother may be very different and require appreciable adjustment on the part of the developing organism postnatally. Thus we know that the rates and intensity of vascular or respiratory activity compared to motor or verbal behavior may vary greatly in different mothers and also this difference may be more marked in relation to one pregnancy than another for the individual woman. These considerations are in agreement with the formulations originally proposed by Mirsky (74, 76) with regard to inborn variations in specific physiologic or biochemical capacities and inborn variations in the acuity of any sensory system; which variations may be expressed as high, mean, or low and each of which may then be in relation to a mother of high, mean, or low "integrative capacity" making possible at least nine baby-mother combinations.

Maternal physiologic rhythms as an object and as a recurring perception at the fetal surface may be *one* of the determinants in development of the so called "body image." In addition, the quality of this surface perception may well be one of the contributors to the functional attributes, including primitive rhythmic rates, of the peripheral and central nervous system. This conjecture is conceivable in view of the evidence presented by Weiss that nerve and ganglion specificity develops out of a retrograde influence ("modulation") from the peripheral end organ (97), the so called resonance relation. This age old problem of the importance of inner growth compared to external stimulation in the development of the properties of the nervous system is still unresolved as recent writings on the subject show (98). The conjecture here would be something like the suggestion made by Carmichael (17) 20 years ago as follows:

"Thus save in time relationships impulses in neurones are not 'caused by' the stimulus. That is *the time* of the presentation of the stimulus and because of the relative refractory phase, *the intensity* of the stimulus are both determiners of the *time functions* of discharge of the activated mechanism and, it may be, only of the time functions."

Adrian (2) expresses a similar view as follows:

"What goes on in the mind is controlled, to a large extent at least, by what is sent into the brain from the sense organs. The particular form of our mental operations may depend more on what was sent in from the sense organs, when the brain and mind were still developing, for what happened then will have helped to establish the connections or associations which we use to make an orderly scheme of what is going on."

Before concluding this part of the paper, I am prompted to point out that I am not in any way talking about maternal impressions or prenatal influence in its too frequent superstitious usage. However, I am suggesting considering a broader, mutual, relationship between the growing fetal organism and the mother of probable significance in the organism's subsequent development. In addition I am suggesting some slight shift in the perspective about these matters gained from the usual laboratory and scientific methodologies, such as expressed by Corner in his informative and delightful essay, *Ourselves Unborn,* (19) as follows:

"In summary, then, and subject only to certain technical reservations, nothing gets through the placenta from mother to child unless it is capable of being carried in solution by the blood, and of passing through the walls of the villi and of their blood capillaries, which together constitute an

exceedingly fine-meshed semipermeable membrane. There is no other means of communication between mother and child. In particular it should be emphasized in capital letters that there is no connection between their nervous systems. Not a single nerve fiber crosses the placental barrier; there is no channel for the transmission of feelings or intentions, moods, memories or ideas. The infant is in fact completely shut off from its own mother save for the exchange of simple chemical nutrients and wastes through a screen so fine that it will pass nothing but the smaller molecules of matter.

"In this regard the proved facts of the laboratory are in flat contradiction to one of the oldest beliefs of mankind. . . ."

There are a number of similarities in this warning of the embryologist and the admonition of Freud concerning the lack of objects to the fetus that I have previously quoted (40).

III. BIRTH

These hypotheses concerning the fetal environment suggest new perspectives in viewing the process of birth. In this context, however, I do not wish to dwell on these matters but will consider them more fully at another time. One of the most thoughtful and stimulating treatments of the significance of birth in the development of the human organism has been made by Greenacre (48, 49).

In view of the thesis of kinds of objects being proposed in this paper, I will point out only a few salient perspectives in reference to birth. First as stated previously (54), the organism may be more or less prepared for birth at 9 months as it is more or less prepared for school at age 6, for puberty at age 12, for marriage at age 21, for the menopause at age 45, or for retirement at age 65. Most considerations of the process of birth, including Greenacre's, emphasize this as being a brief tumultuous episode in the life of the individual, variously termed a caesura, a hiatus or the great chiasma. However, recent studies of the normal physiology of the pregnant uterus, particularly the work of Reynolds (78–80) and Alvarez (6) indicate that the birth process occurs over a number of days or even weeks and is not the brief occurrence which evident parturition in the mother or the appearance of the newborn babe would suggest. It seems likely, as with most significant changes to which the organism has to adjust, that there is a period of practice or trial before the irrevocable event occurs.

The main point I wish to propose at this time in relation to birth is a different perspective with regard to the quality of the change which may be experienced by the fetus-neonate. All students of this problem assume that the fetus passes from an environment of low stimulation to an environment of high stimulation from the ease of the womb to the toils of the world. In view of the premises here proposed, it is conjectured that the newborn may pass to an environment of lower surface stimulation and at the same time is separated from a known, consistent, repetitive kind of stimulation. This change may be like spending all day in an organized boiler factory and then going out in a quiet street. Or perhaps it is more like a person who has lived all his life in a big city, next to an elevated train and who then goes to the country with all its strange lack of familiar noises. The new stimuli are different, less persistent, exotic, and most important are relatively random.

IV. NEONATAL OBJECTS AND RELATIONSHIPS

As a sequel to our discussion so far and as a prelude to this section of the paper, it is fitting to quote the final passage from Paul Weiss's book, *Principles of Development* (96).

"There are many advantages which the study of embryonic functions offers over that of the adult body; embryonic func-

tions are more primitive, hence more schematic, and show the crucial aspects in sharper relief. Moreover, by choosing the proper stages, it is possible to get an unobstructed view of certain vital phenomena while they are still in pure and, as it were, nuclear form, not yet obstructed by a host of complicating factors of more recent appearance. To get rid of the latter the physiologist must apply elaborate surgical and pharmacological measures while the embryo might have presented him with the unobscured situation from the beginning. Apart from the work on the nervous system, advantage has been taken of this fact only in the study of heart function and a few other scattered instances. A systematic exploitation of this promising field of Embryonic Physiology has not yet even begun."

I have suggested viewing the vascular relationship of the fetus with the mother as a kind of object relationship and considering the mother's physiologic activities as affording a kind of repetitive object perception at the fetal surface. This hypothesis leads to the inference that the fetus may be exposed to a surface stimulation of less rather than more intensity in passing from the prenatal to the postnatal state.

It has been noted by a number of investigators (46, 49) that the neonate is relatively insensitive to a variety of stimuli for 2 to 10 days after birth. Gesell describes the neonate as "quasi-dormant" (46). This relative insensitivity of the neonate is noted by Greenacre (49) and attributed to the effect of the birth experience and subsiding as cortical integration resumes or develops. While a variety of explanations of this observation may be pertinent, most approaches to the apparent cutaneous insensitivity of the neonate seem to be retrospective. That is the neonate's insensitivity is viewed relative to later sensitivity. It is only after a number of hours or days postnatally that the baby becomes responsive, or so responsive, to sources of pain, or a variety of tactile or sound stimulation as it then continues to be during most of its later life. So it is reasoned that the baby is transiently insensitive during the first few days postnatally. Another explanation of this apparent cutaneous insensitivity is that the neonate is not yet perceptive and therefore not yet responsive to the kinds of stimuli the experimenter expects and uses.

From the assumption of the perception at the fetal surface, I would expect that the neonate would be responsive mainly to variations in frequency and perhaps intensity of some repetitive stimulus and would have to "learn" within this perceptive set the significant variations of relatively random stimuli experienced postnatally. It might be informative to examine the responsiveness and variations in response of neonates subjected to stimuli of constant quality but of varying frequency or intensity, similar in nature to the studies of Lourie (70) with a metronome in older children.

I assume then that the familiar perceptive set of the neonate, from prenatal experience, is a fairly consistent repetitive surface stimulation which represents a kind of object expectation and which provides the background or foreground for perception of stimuli at the postnatal boundary or environment. This set has developed from experience with the repetitive maternal physiologic activities already described and it is in or on this limitless sea of stimulation that there must accrue the "islands of consistency" of which Escalona speaks (33). Perhaps it is on this monotonous plain of stimulation and perceptivity that the particular landscape of the postnatal environment develops. The choice of metaphor may depend on whether I am in deep water with these conjectures or have some grounds for the premises proposed.

MATERNAL PHYSIOLOGIC ACTIVITIES OR THEIR EQUIVALENTS AS OBJECTS POSTNATALLY

Object relationships in the neonate and infant have been perceived largely though the model of the oral feeding experience,

breast or bottle, and this has been a main focus of neonatal relationships particularly is psychoanalytically oriented theorizing. The other neonatal experience of import and concern has been and is respiratory behavior, which, although less obvious and without the sentimental attribute of baby-mother relationship that surrounds the feeding experience, nonetheless has an attribute of urgency compared to oral feeding. These kinds of experience, breathing and oral feeding, are of great significance in the character of the infantile development and develop almost simultaneously. However, in keeping with the prospective approach in this paper, it may be necessary and fruitful to consider these kinds of experience separately, and only after considering certain other object relations of the neonate which may be more directly related and continuous with those already conjectured during fetal experience. Therefore we will consider maternal physiologic activities postnatally, and then breathing and then touch upon the feeding experience. This fragmentation for clarity will be made, while keeping in mind that we are discussing simultaneous processes in the baby-mother relationship.

Babies nurse, sleep, cry, nurse, sleep and also urinate and defecate. These are the high points in our perception of the baby. Babies also breathe and they also experience contact with the mother or other adults; holding, patting, rocking, walking, vocal sounds, singing, etc. All this contact occurs at times during and at times separate from the actual feeding experience.

A corollary or sequel to the suggestion that there is a kind of object perception at the fetal surface provided by the mother's physiologic activity is the proposal that this same kind of object or perception of the mother continues to be perceived postnatally during the contact relationships mentioned above. That pressure sensations experienced during intrauterine life incident to the mother's walking may be reexperienced postnatally by the baby, while being walked, is fairly evident and has been readily considered by many observers. However, it is my premise that the repetitive perception incident to the mother's vascular pulse and respiration, described as significant for fetal experience, continues postnatally incident to perception of the mother's respiration and vascular (including cardiac) activity. The only reference that I have found to the mother's respiratory or vascular activity being a possible object perception for the neonate is the following statement by Hoffer (59): "In the sucking experience the sensation will be reinforced by not-body objects, the milk, the breast, the bottle, and the mother's grip, breath or heart beat." Here he views these latter sensations in the traditional perspective, as incidental to or augmenting the oral sucking experience.[6]

However, I assume, that certain rhythmic perceptions provided by the mother may constitute the earliest object perception of the mother to the neonate and are a continuation of the qualitatively similar prenatal surface perceptions. These afford a kind of object recognized and expected by the neonate. I point out that the location which affords the best opportunity for perception of these maternal activities is the chest and this in the human is the location of the breasts. It is also noted that most women are right handed, which means that they hold the baby with the left arm in giving a bottle leaving the right arm free, and also they usually hold him over the left shoulder for bubbling, rocking, patting, walking. Cardiac pulsation is transmitted with greater intensity in these positions. Blauvelt from her study of the mother-newborn relationship in goats emphasizes that "the anatomies of mother and kid fit together beautifully" (16). Here I am stressing not only the fitness of the mother's anatomy but also her physiology.

[6] Since writing this paper I have found that these factors in early relationships have been considered by Meerloo (73). His paper brought to my attention similar ideas proposed by FitzHerbert (38, 39).

While perceptions of maternal vascular pulsations and respiratory movement in themselves provide a kind of object perception familiar to the neonate, there are other similar repetitive stimuli to which the neonate is exposed by the mother. One of these is rocking, which, although not as common as in years past, still occurs *via* the chair or cradle. The other is patting, usually the back of the baby, while it is held over the mother's left shoulder and frequently rocked or walked at the same time. Preliminary observation of the rates of rocking and rates of patting indicate a wide difference between the frequencies of these two behaviors on the part of the mother. Rocking tends toward synchrony with the mother's and/or baby's respiratory rate while patting approximates the mother's and/or baby's cardiac rate. This correlation would be susceptible to investigation in different babies, different mothers and different baby-mother relationships.

While the mother's respiratory and cardiac activity may be more influenced by the neonate's behavior postnatally compared to the prenatal conditions, I assume that repetitive recurrence of this kind of object perception to the neonate is still predominately one sided and only a very low order interreaction. Even so the rates of these perceptions of vibration or pressure emanating from the mother will vary and may have some "meaning" postnatally as suggested prenatally. I conjecture that these perceptions, incident to the mother's physiologic activities, constitute a major element in the phenomenon of contagion discussed by Escalona to which I have already referred. In view of this account of the baby's postnatal perception of the mother, it is fitting to continue with Escalona's account of these matters previously quoted (31).

"By contagion, I mean those processes whereby a feeling state transmits itself from mother to baby, as when an infant cries when held by an acutely tense and anxious person but seems quite content when held by one who is relaxed; or, when a baby cries but then settles down merely upon being spoken to and patted in a reassuring manner. As far as I can see, contagion is never fully subject to voluntary control by the person from whom it emanates. An excited, worried mother may try to convey reassurance, but the baby, if he is susceptible to contagion, will respond to her actual feeling state. On the other hand, a person who really feels calm can, if she is at all skillful, intentionally convey a sense of calmness to the baby."

In another context Escalona says:

"We have all thought about the curious fact, reported and acknowledged by the majority of persons who have observed children, that a mother's feeling state, including altogether unconscious material, exerts a marked effect upon the baby's response and the developing relationship. I find these phenomena least mysterious and most amenable to systematic exploration in the light of the concept of contagion as here sketched. It stands to reason that whatever the adult is really feeling is what is contaged, if you will excuse so ugly a word. It is also plausible that a mother whose energies are heavily engaged in holding at abeyance anxiety aroused by unconscious conflict would find it more difficult to direct herself wholly toward the baby, as seems to be necessary when contagion is used deliberately. I also think, and I mention this only in an attempt to activate your own memories and associations in this context, that this is what we mean when we speak of distance between mother and baby. Such emotional distance can be observably present while a mother breast feeds her baby or kisses him. One way of putting what we see, or rather what we feel to be lacking in what we see, is the absence of the undercurrents and vibrations denoting the presence of contagion. I feel like apologizing for such

sloppy use of vague words like "vibration," but I am simply unable to go beyond a kind of imaginative description and speculative approximation of what I think is a clearly observable reality" (34).

Questions of the apparent ugliness or sloppiness of wording should not be a matter of concern in depiction of what I presume Escalona is trying to describe. Whatever may be the object perception of the neonate this may be vastly different from anything that can be expressed in familiar words, and is likely much more esoteric than the term "preverbal" implies. It may be that the variations in the object world to the neonate can only be expressed vocally as variations on the theme of a familiar hummed lullaby. To be sure this may be vague but it does not necessarily mean that any more scientific, accurate, or appropriate expression will be afforded by the anatomic or physiologic terminology for the amoeba, the nomenclature of acoustical physics, or the formulas of cybernetics.

This has been an extension of my main postulation developed in this paper. Namely, that there is a prenatally experienced kind of object perception incident to the mother's physiologic activities and that this continues postnatally with much the same quantitative and qualitative characteristics and provided by the mother by much the same mechanisms. This involves the assumption that there is a kind of object perception which bridges the so called caesura of birth, and a kind of object perception which is the model for all those to come later, and is the key object of the developing organism for perhaps a period of six months—one, two or three months before birth to one, two or three months after birth, but is still operative thereafter.[7]

[7] Since writing this paper there has come to my attention a pertinent panel discussion, chaired by Kris, on the Problems of Infantile Neurosis (The Psychoanalytic Study of the Child. IX:16, 1954). Much of the discussion centers around rhythmic behaviors of the infant, chiefly as manifested in rocking and head knocking. These matters are discussed in greatest detail by Greenacre and Anna Freud.

Greenacre introduces the concept of two types of rhythm, the one repetitive and regular with a lulling, familiar quality, the other accelerating, crescendo, orgastic and gratifying. This formulation presents a significant contribution, but I would add that rhythmic activity manifested in any system or level of organization, vascular, respiratory, motor, shows three qualitative variations, the one accelerating and perhaps orgastic in character, the second relatively regular, constant and soothing, and in addition the third a decelarating rhythm, decelerating even to the point of cessation, which eventuality either is not observed, is ignored or is "lost" in the expression, primary narcissism.

While Greenacre's basis for formulation stems largely from psychoanalytic observation of "borderline" patients, Anna Freud affirms the significance of rhythmic manifestations as fairly "normal" behavior in young children. In this connection she says, "On the basis of direct observation and reports on behavior, I believe now that rocking and head knocking are much more frequent occurrences among normal children than we used to assume at times when both activities were reported almost exclusively from the observation of defectives. Dr. Greenacre mentions their possible connection with birth conditions. I want to go one step further and suggest that the answer to this problem has to be sought for not in distinctions between pathologic states but in so far unexplored interrelations between intrauterine and extrauterine life."

POSTNATAL RESPIRATORY ACTIVITY OR BREATHING

One of the first and probably the most urgent of the newborn's activities is breathing. Beginning of this function is requisite to the neonate's acquiring oxygen and expelling carbon dioxide on a more highly integrated, more autonomous level of organization than took place prenatally. This step in maturation is necessary for the survival of the organism chiefly because of the biochemical, oxygen, and carbon dioxide exchanges which pulmonary function subsumes. It is chiefly in this light that breathing usually has been considered. In addition it has been considered in psychoanalytic theory in the frame of reference of oral, anal, or phallic behavior and organization. With the prospective, not retrospective, orientation we are using, I

would suggest additional ideas with regard to breathing in the organism-environment economy of the developing neonate.

In the preceding section I have indicated that the neonate continues to have available the repetitive perception of the mother's physiologic activities to which it had been exposed for some time prenatally. Even so such perceptions of the mother will be less continuously available postnatally compared to the prenatal condition. I have indicated that these physiologic activities of the mother provide a recurrent cutaneous, sensory and/or kinesthetic perception. Now such a recurrent sensory and/or kinesthetic perception is an important component of breathing in addition to and along with the biochemical component usually emphasized. Just as the fetus does not give up the fetal mechanism of acquiring oxygen from the mother *via* the vascular environment until it is ready to take over this function by other more autonomous means, so it does not have to begin to give up the physiologic rhythmic perceptions provided by the mother until it is prepared to begin to supply these sensory and/or kinesthetic rhythms to some degree by itself also through breathing activity. While we have previously been talking about a surface perception to the fetus-neonate which is provided *by* the mother and is motor-neural and vascular-neural in mode of transmission, we are now in addition considering a surface perception provided by the neonate itself and motor-sensory or sensorimotor in mode of transmission. Even so I consider that the neonate may not be able to differentiate for a while between the surface perception derived through these two different modes of derivation. However, this is an inability to distinguish as yet between two different kinds of objects and two different kinds of object relationships. The recurrent surface perception incident to the mother's physiologic activities or to the neonate's breathing are both I assume differentiated from "self" even though there is not yet differentiation of one kind of object from the other. As differentiation of one of these surface perceptions from the other develops, I assume that a change in what Hoffer (59) terms "self-me" also occurs. However, at no time will there be "normally" any consistent state of undifferentiated self-me-object but only gradations of self-me in relation to gradations of kinds of objects. In reference to this matter Hoffer speaks of "the spread of the feeling of self over the infants body, in which the self is housed" (60). The concept of the individual's own body as object, and the precedents for this viewpoint, has recently been reemphasized by Szasz in his considerations of the problem of pain (95).

BREATHING AS A MOTOR MEANS OF CONTACT AND SEPARATION IN RELATION TO OBJECTS

From our prospective orientation we have considered breathing as a function providing not only requisite autonomous biochemical exchange but also an autonomous recurrent surface perception for the neonate. This approach suggests further functions of postnatal respiratory activity which I think are significant but may complicate and tax the differentiating abilities of the presumably helpless infant.

As mentioned before breathing has usually been considered in psychoanalytic theory through the model of oral, anal, or phallic function. This is most likely related to psychoanalytic focus on these stages from retrospective reconstruction. Psychoanalytic theory has been preoccupied with what goes in or out of the mouth; breasts, nipples, fingers, milk, food, vomitus, spit, cries, sounds, words, and air. While air, or oxygen and carbon dioxide, go in and out of the mouth or nose this fact is relatively incidental compared to oral behavior related to food and sucking. Even so breathing has been considered in its psychologic significance as most basically like

oral behavior. Thus Fenichel (36) says:

"The first positive instinctual behavior toward a desired object consists in diminishing the distance between oneself and the object and finally in swallowing it (later limited to taking in into the mouth). The first negative instinctual behavior toward a repulsive object consists in increasing the distance and 'spitting it out' (later condensed with eliminating it according to the pattern of defecation)."

In another context he says (37),

"Inhaling the same air as another person means to be united with him, while exhaling means separation."

These statements represent the premises for most psychoanalytic thinking with regard to the psychologic significance and meaning of breathing and there is ample evidence to support these premises for psychic economy at a stage later in the development of the child than we are considering here for the neonate. I point out that the sensorimotor component of oral feeding behavior or sucking is oral and perioral in location, *while the sensorimotor component of breathing is predominantly localized in the chest, abdomen, trunk,* even though air goes in and out of the oral aperture. This means that the autonomous recurrent sensory perception incident to breathing, is a recurrent perception located in the chest and abdomen, chiefly the ventral surface of the neonatal trunk.

Furthermore breathing provides with its motor component a facility for varying surface stimulation in contact with objects, which to us observers, are not a part of the infant's own body. This means that breathing provides a means for the fetus to relate to objects through tactile trunk perception. I suggest that this precedes and may be one of the bases for later developed "ideas" of object relationship incident to inhalation and exhalation. Thus taking in of air, inspiration, is accompanied by closer tactile, trunk contact, "a reaching out to" an object while getting rid of air, expiration is accompanied by more distant tactile, trunk contact, "a withdrawal from" an object.

I have already pointed out that babies do not nurse all the time even though many mothers may insist that this is so and they do not sleep all the time even though many fathers may wish that this were so. Nor is all of their experience confined to eating and/or sleeping as the formulations of Lewin presuppose (68). As I have done repeatedly I turn to Escalona's observations.

"It may have been a mistake to choose feeding and sleeping for the emphasis on what kinds of experiences babies may have, for these are the two functions which everybody thinks of as being significant during early infancy. The most important thing I have learned about young babies is how much else there is to their daily life, and how many responses and adaptations they are called upon to make other than those connected with these vital functions."

"Almost all of the time, the baby is in contact with the outer world through his skin. Diapers, shirts, gowns, blankets, sweaters, bonnets, sheets, the mother's hands, the mother's clothing, water of different temperatures, cottonwool, oil, drafts and breezes, soft and hard surfaces, all approach and withdraw from his skin. What this may mean for the excitation-quiescence and the pleasure-displeasure elements in his life depends both on what his mother is like and his general life circumstance, and upon what his skin is like, physiologically speaking" (35).

With all this I agree including the fact that these objects of the outer world "all approach and withdraw from his skin." At the same time I suggest that *via* the activity of breathing the baby, on his part, "approaches and withdraws" from many of these objects with associated variation in cutaneous or kinesthetic sensation of the trunk. As with most kinds of object relationships, the developing organism is a

determining participant, the least so with the surface perception described prenatally.

These premises focus upon three kinds of surface perception for the neonate: (1) the continued perception of the mother's physiologic activities, (2) the cutaneous and kinesthetic perception incident to breathing itself, and (3) cutaneous and kinesthetic perception in contact with "external" objects. All three of these kinds of objects and object relations have different qualities which will be discussed more in detail later. For the moment it is emphasized that these are object relationships which are "trunk centered" so to speak.

THE CEPHALO-CAUDAD POLARITY IN ORGANIZATION OF EMBRYONAL AND POSTNATAL DEVELOPMENT

So called cephalization is evident in evolutionary development and in ontogenetic development at various levels of organization. The accelerated growth and functioning of the cephalic structures compared to caudal structures has been noted for years in human embryogenesis. Many reports have noted a parallel cephalic precocity in psychic organization. Frequently this similarity has been used in support or explanation of some psychic organization and at times to give biologic substance to psychologic phenomena. While this comparison of a polarity in psychogenesis and embryogenesis is useful and valid as far as it goes, the parallel has not been carried to its logical and factual conclusion.

With respect to this matter in embryogenesis Patten (77) speaks as follows:

"Even casual inspection of a series of embryos of increasing age makes it apparent how rapidly the cephalic region is expanding. It is easy, however, to overlook the part played by the more caudal portions of the embryo in this cephalic growth. From the region of the primitive streak, cells are continuously being pushed forth into the growing body, but we see the results of growth activities in the increase in size of other regions. Paradoxically, the primitive streak itself does not become larger by reason of its own activity, for the cells there proliferated promptly emigrate and the primitive streak itself becomes a relatively less and less conspicuous structure."

This means that in embryogenesis, after development and organization of the initial embryonic disc and more specifically the primitive streak, there occurs growth at the cephalic end of the embryo and at the caudal end. In this subsequent growth at both ends, so to speak, that at the head is always more precocious than that at the tail. However, that which lies between, the primitive streak, has been more precocious than either. This is overlooked as noted by Patten partly because the primitive streak itself becomes a less and less conspicuous structure. In addition to these anatomic facts, this oversight is compounded by the observer of embryogenesis who tends to be engrossed with invaginations and protrusions developing at the cephalic or caudal end of the embryo. However, in embryogenesis there is a dominance progression from the center, to the head, to the tail.

Now in consideration of the genesis of psychic organization emphasis has also been placed on the earlier organization of cephalic function compared to the caudal, while overlooking what goes on relatively inconspicuously in between. This has been due to the fact that psychologic observation, particularly psychoanalytic, has been preoccupied with apertures that move and make noises, and with protrusions manifesting activity. This has prevented awareness or consideration of the "trunk centered" behavior and perceptions of the neonate, which are emphasized here, and which transpire with relatively inconspicuous breathing and "mere" contact with the mother.

Consideration of these "trunk centered" cutaneous and/or kinesthetic perceptions of a kind of object incident to breathing suggests that breathing deserves a place along-

side of oral, anal, and phallic activity in developing psychic economy. The kinds of cutaneous perception and the kinds of object relation incident to breathing and contact, and chiefly "trunk centered," if permissable assumptions, may be important considerations in understanding a number of psychosomatic disorders and psychic symptomatologies. These would include bronchial asthma and other respiratory disorders such as hyperventilation; certain hysterical, hypochondriacal and delusional symptoms in the chest and abdomen; the changing patterns of symptoms (65) and also the so called Isakower phenomenon (63). Spitz has noted the psychiatrists neglect of this large trunk part of our body, particularly the powerful and intricate musculature subsuming postural function (91).

These cutaneous object perceptions incident to breathing may well be of significance in the developing "body image" along with the perceptions of maternal physiologic activities as previously suggested. Also the neonates own vascular pulsations may contribute to development of the "body image."

As repeatedly stressed by Engel there are many indications that biologic process and action precede and circumscribe the psychologic expression thereof (25). Further evidence of this has been shown by Engel, Reichsman and Segal in their recent contribution through the unique study of an infant with a gastric fistula (27, 28). Some of the formulations presented here may be of importance in comprehending and explaining some aspects of the biologic, psychologic continuum and the transition during development from the more purely biologic to the biopsychologic. The cutaneous "trunk centered" perceptions proposed may afford the basic perceptive anlage for psychologic ontogenesis. This would seem to have more substance than the premise that the earliest perceptive gestalt is the oral cavity which I presume becomes defined and involved somewhat later.

Consideration of these recurrent surface object perceptions to the neonate incident to maternal physiologic activities and autonomous breathing preclude the necessity of assuming "regression" to a prenatal state with the occurrence of intrauterine-like perceptual or behavioral phenomena.

CRYING

The formulations being developed here suggest certain perspectives regarding crying in the newborn which I will set forth briefly at this point. In spite of the prevalence and agony of crying of the baby, surprisingly little study of this manifestation either in the child or adult has been made. The pioneer studies of Aldrich (3–5), more recently of Illingworth (62), and of Stewart (92, 93) are the only systematic considerations of crying in newborns which have come to my attention. The meaning and purpose of crying following birth is diversely interpreted by different observers. As editorialized recently, "To the physiologist it is simply a neat mechanism for assuring deep respirations, but to the psychoanalyst it is a vigorous protest against an uncomfortable ejection from the peace and security of the womb" (24).

Since the original observations of Darwin, (20) crying has been considered mainly in respect to its facial motor components, perioral and periocular. These are the sites of the most evident expressions of crying, in particular an oral noise and ocular weeping. However, tearing or weeping does not generally occur in the baby until the third to fifth week. Crying in the baby has generally been considered as protective and protesting and is described by Aldrich as a negative response. It is also considered as a mechanism for discharge of emotional tension, anxiety or aggression. The "need" or the specific quality of the baby's distress which eventuates in crying has generally been assumed to be food hunger. As mentioned the physiologist tends to think of crying as facilitating satisfaction of oxygen hunger.

While crying is generally associated with its facial, oral and ocular, manifestations

and with oral nutritional need, crying also includes major breathing components (4, 62). Crying involves an increase in the depth and intensity and/or rate of breathing. This is evident either in the deep, short inspiration with prolonged expiration or in sobbing or combinations thereof. This constitutes the major motor component in the eventuating vocal cry. While crying is associated frequently with food hunger, Aldrich found this demonstrable in only about a third of the instances of crying in the neonate while another third of the crying episodes were related to apparently noxious stimuli, vomitus, soiled or wet diapers, and the remaining third were not due to any apparent cause. Illingsworth ascribes "loneliness or a desire to be picked up as an important cause of crying in the first three months" and notes the mistake of thinking that all the baby's crying is due to hunger. Aldrich (4) emphasizes what he calls more or less negative causes "as need for fondling and lack of rhythmic motion." All of these students of the problem describe the apparent influence of contact itself with the mother or nurse in cessation of the baby's crying. Stewart describes the importance of the mother's emotional state in the effectiveness of this relationship.

Now in considering the "needs" of the fetus we have talked in terms of "oxygen hunger," and "food hunger." In examining the kinds of objects for the fetus we have talked in terms of concentrations of oxygen and concentrations of glucose at the vascular environment and also of the recurrent perception at the fetal surface. For the neonate we have dealt so far only in terms of oxygen and the continued recurrent surface perception both of which are now autonomously available and modifiable through breathing activity. That is to say increase or decrease of oxygen and also the rate and intensity of the surface perception eventuate with changes in breathing behavior. I suggest that "distress" in the neonate related to lack of oxygen or excess of carbon dioxide primarily determines increase in breathing rate and depth with resulting adjustment. Distress in the neonate related to lack of the expected surface perception also determines increase in rate and depth and intensity of breathing which at times autonomously affords readjustment. When distress continues further increase in rate and/or depth and intensity of breathing occurs eventuating in vocal noise or crying and then contact with the mother's physiologic rhythms due to her motor behavior may afford readjustment. When distress still continues, as would be the situation if food hunger is present, readjustment would not take place, and continued increase in rate and/or depth of breathing with crying would continue until food hunger is satisfied by additional motor behavior of the mother, offering the breast or bottle. These considerations point back to the early observations of Ribble in which she repeatedly emphasized three types of activity and need of the newborn, a need for oxygen, a need for food and also a "need to feel" or "hunger for tactile experience" (82–85).

This formulation suggests that crying may be as fundamentally associated with the lack of the surface object perception proposed here as with food hunger or with food as we observers think of it and as the baby may come more directly to associate the reaction of crying. This attributes to the behavior of crying, or the breathing component thereof, some positive autonomous adaptive qualities other than those of protection, protest, and random discharge of "tension." It is further considered that there are probably changes in breathing activity during the baby's sleep serving autonomous adaptive ends similar to those ascribed to sucking movements during sleep.

THE DIFFERENT QUALITIES OF THE RELATIONSHIP TO THE SURFACE OBJECT PERCEPTION IN THE NEONATE

We have been presuming a cutaneous or kinesthetic sensation at the neonate's sur-

face as a kind of object. This recurs incident to the mother's physiologic activities when the baby is held by the mother; it recurs incident to the baby's breathing activity alone and when held by the mother and also it recurs incident to the host of approaching and withdrawing behaviors available to the mother, most grossly leaving and returning to the baby or putting him down and picking him up. While it is likely that there is or readily develops a difference to the infant in the quality of the sensory surface perception ensuing with these different processes, we will assume transiently for purposes of examining the processes that the recurrent perception is the same to the baby.

For the present we will consider three main types of process or object relationship for the baby, presuming the surface perception as a kind of object and an essential object for the developing neonate. First the mother's physiologic activities, as we have assumed prenatally, continue to provide a recurrent perception though less consistently so, since they occur only when the baby is in direct contact with the mother. This relationship with the mother (purely a surface perception) as already discussed is predominately a receptive relationship on the part of the neonate, probably mainly mother to baby, and vascular or motor on the part of the mother and neural on the part of the baby. As such this is a very low order interreaction and may not even be an interreaction according to the definition given. This is almost exclusively an afferent neurologic process on the part of the neonate with no determinable corresponding efferent component which can effect the source. The recurrence rate and intensity of this surface perception, while varying to some degree, is in any brief unit of time relatively constant. What variations in rate and intensity that do take place are not brought about in any appreciable way by the neonate initially even though this may come more and more to take place during neonatal development.

Secondly, the baby's own breathing activity is a means of experiencing the surface perception. In contrast to the above kind of object relationship, this activity constitutes the baby's own physiologic mechanism and movement of its own body surface, alone or in contact (to us observers), affording a kind of object. This process or relationship with the object is sensorimotor or motor-sensory on the part of the neonate. It constitutes a neurologic process of the fetus with both afferent and efferent components even though modulated by biochemical factors.[8] Most significant in comparison to the previous relationship this is an interreaction with motor efferent response, in part incident to a "previous" surface perception, affecting the next recurrence of the surface perception. In addition while the recurrence of the surface perception may be inconsistent and variable compared to that incident to the mother's physiologic activities, the changes in rate and intensity are predominantly determined by the neonate, no matter how "clumsily." Even though the rates of recurrence may be inconsistent compared to that previously experienced and still experienced in contact with the mother's physiologic activities, the rate of the neonate's breathing is relatively rapid and the period of recurrence lies within the range experienced incident to the mother's respiration and vascular pulse.

Thirdly the recurrent perception at the surface incident to the baby's behavior and the mother's behavior subsumes still another type of relationship. The process of this relationship with the recurrent surface

[8] The still debatable problem of the sources of respiratory activity was noted by Barcroft (11) many years ago as follows: "... Are the chemical and the nervous stimuli to the respiratory centre really, in the same sense, stimuli? Or is one (the chemical) an increased lubrication of the machine, whilest the other (the nervous) is an increased effort on the part of the man who operates it? Of what is each stimulus capable in the absence of the other? What is the relation of the two combined to each separately? ..."

perception (the mother) is a reciprocal affair involving an afferent and an efferent component on the part of the baby which is more complex than that assumed in the second relationship above. Thus the usual efferent reaction involves crying or other reaction on the part of the baby, which I assume requires more highly integrated function than the efferent component of breathing alone. The process of this kind of relationship also involves an afferent sensory component and also an efferent component on the part of the mother, both components frequently highly complex. Thus (to us observers) this third kind of object relationship involves a neurologic afferent and efferent infant phase and an afferent and efferent maternal phase. Even so to the baby I assume this is a matter of delineating modes of its own behavior in relation to recurrence of a surface perception. While the baby may differentiate this surface perception of contact, with return of the mother, by some quality of the perception compared to those considered above and perhaps by the comparative mode of efferent behavior affording recurrence, the most significant characteristic of this process of object relationship to the baby may be the wide range and duration of recurrence which is involved. Thus compared to the recurrence rate experienced from the mother's physiologic activities, and the recurrence rate usual and determined with breathing function, the periods of recurrence incident to the baby and mother's behavior is "infinite" even though the range is great. This fact is so in view of anatomic, physiologic, and mental attributes of the baby-mother unit. As mentioned previously there is an equivalence of distance or space and time as a recurrence of a perception or object.

These are three kinds of relationship with the surface perception, the object, the mother which I propose the developing neonate experiences. Whether the quality of the object perception differs, and when and how I will not conjecture. However, the afferent component of or for the baby is different in all three kinds of relationship and the range and consistency of recurrence is different in all three processes. I would describe these three qualitatively different relationships as automatic, autonomous, and mutual. The automatic continues while the autonomous begins to be necessary and develops, and the autonomous is developed and available as the mutual becomes necessary.

ORAL FEEDING ACTIVITY

So far we have said nothing of mouth activity of the baby nor the breast or bottle provided by the mother. This is so because with the prospective approach to these matters, I assume that these orally circumscribed processes and objects are less well delineated compared to those previously considered.

First to consider sucking. This is a sensorimotor interreaction providing a way of relating both to the baby's own mouth surface and to the nipple. This sensorimotor activity is variably patterned at birth and generally maturates rapidly. Other than breathing this is the main behavior which is repeatable by the neonate, but most important it provides after breathing the only motor reaction which is followed by a recurring sensory perception or object of the kind we have been considering. This is so whether sucking includes only the mouth itself, the tongue, the lips, or whatever comes into the mouth by chance or by design, a blanket, a finger, a bottle, a pin, or the breast. All of these latter "to us external" objects may enhance the sensory return of sucking and enhance the kind of object of this stage. However, in the majority of instances what gets into the mouth is the nipple of a bottle and in the minority of instances it is the nipple of the breast. Either of these is more satisfying for sucking because their presence in the mouth also means contact with the familiar physiologic activities of the person whom the baby will someday come to know as "the mother."

But such object perceptions and relationships involving autonomous sucking, autonomous breathing and the mother's physiologic activities, even with satisfactory respiratory exchange are not persistently pleasurable since these do not supply satisfaction of food hunger. By chance or by design the nipple of the breast or of the bottle which is sucked usually contains milk which *via* the gastrointestinal tract supplies nutritive needs and satisfaction of food hunger. Then the baby can settle down to enjoy his object world of perceptions incident to the mother's physiologic activities, rocking, walking, talking and incident to its own breathing, and go to sleep, without the necessity of bothering with those alien activities of sucking, or those transient encroachers the breast or bottle. Even so, like a prepubescent boy who does not want to bother with the girls he will learn to love them and include them as one of the most important in his sphere of objects. Oral feeding behavior in the prospective approach presented here may be one of the first instances of "progression for the sake of regression" as recently discussed by Balint (9).

Oral sucking behavior then is viewed as affording the initial cephalad sensorimotor activity providing autonomously a sensory object perception comparable to the similar "trunk centered" facility incident to breathing already discussed. Oral, mouth behavior is to food hunger what respiratory behavior is to oxygen hunger. Each interreaction affords supply of necessary but different biochemical constituents and each affords a necessary but different mode of relating to objects both the neonate's own body and the mother.

The oral feeding experience has been the model for theories both of earliest psychic function and particularly earliest object relationships. From this has come the focus on the alimentary relation between baby and mother. This has been noted by Greenacre (50) and emphasized more by Benedek (14, 15) in her significant formulations with regard to the mother-child symbiosis (13). Alimentary as employed by both of these investigators implies the connotation of nutritional and gastrointestinal. It is my premise that there are significant modes of function in the baby-mother symbiosis other than the alimentary or gastrointestinal during human ontogenesis to be considered of equal importance in psychophysiologic development. Some of these processes I have described undoubtedly with some errors in hypothesis, but, I think, with appreciable biologic substance and basis and I hope with some usefulness.

While the relationships and kinds of objects presented for consideration are chronologically speaking preoral, they are also in a sense "extra" oral and continue to provide both a means of relating to objects, and kinds of object perception even after the maturation of oral behavior.

V. SUMMARY

Getting the baby to breast or on the bottle is a good point at which to stop for a while in this train of thought. I have presented some considerations and formulations with regard to fetal-maternal and neonatal-maternal ontogenesis. These have included facts, processes, and events as well as kinds of objects for the developing human organism. Much of what has been presented has been disregarded in observation and interpretation of the mother-child relationship and in attempts to comprehend the biopsychologic development of the individual. In this respect I am in agreement with Balint's appraisal (8), "The form of appearance drowned the essence: *what presented itself as loud, forceful, or vehement, has been valued as important, what happened quietly as unimportant.*"

The material considered was initiated by the observation of concurrent somatic and psychologic manifestations in patients with leukemia and lymphoma. The formulations have developed largely through observation

of young children with leukemia with their mothers. To be sure these young patients are severely "regressed" both physically and psychologically, and their relation with their mothers may show distorted kinds of processes of relationship with the mother compared to the more usual child-mother relationship. Even so, preliminary consideration of the more usual baby-mother relation indicates that the factors presented here may well be important, and to be considered in perspective in investigation of the mother-child unit. However, it should be noted that the processes under discussion present themselves not as visual or auditory stimuli but as tactile or kinesthetic stimuli. Therefore increased accuracy of vocal or other sound recording, or controlled observation of the investigator will not elucidate these phenomena. Only by perceptive observation of mother and own baby, mother and any baby, any adult and any baby, may evidences and inferences of these processes of relating be derived. Further elucidations may eventuate through direct relationship of the investigator with a baby. But an observer, camera, or sound recorder will not see or hear what the baby, mother, or investigator may be perceiving.

In a discerning address Engel (26) suggested the probability that psychologic observation of patients with neoplasia would lead to pertinent insights into psychologic phenomena as well as increased understanding of patients with neoplasia. He also emphasized the need for some elucidation of the physiology of the mother-child unit. This inquiry has provided some start toward these goals. The material and formulations presented furnish some additional foundations for understanding the biopsychologic continuum. More detailed elucidation of these changes and when and how they transpire I leave to others and my own further observations and interpretation. A main premise has been that there are very early kinds of objects perceived by the developing human organism; objects discerned *via* somatic rather than psychologic processes; processes, biochemical and physiologic, affording to the organism affective changes in the sense of variation in degree of tension although not necessarily differentiated into the categories of later affects; and both the object and the relationship being personal in that it continuously, through a variety of modalities, includes a person, the infant's own body and/or the mother.

These object relationship processes hypothesized may be of importance in understanding qualities of the usual patient-doctor relationship which is mutually visual, mutually auditory, and in addition mutually tactile. These considerations in addition may afford insight into attributes of the usual relationship management of medically sick patients and those with the more generally appreciated psychosomatic disease. Initial systematic study of the therapeutic process with these patients has been made by Margolin (71, 72), Kaufman (64), and Engel (29).

In another context I wish to discuss these formulations with respect to those derived by Michael and Alice Balint through their separate and mutual investigations (7, 8). Their appreciation of the earliest phases of object relationship has most closely approximated what I have come to assume. The formulations presented afford some explanation, but may require some readjustment, of the hypothesis of "the oral triad" formulated by Lewin (69). Lastly, I note that the premises developed here do not disagree, as much as initial reading may suggest, with the original insights of Freud, in particular his discoveries of the functional attributes of man's mental apparatus, designated the Id and the Ego (41).

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ELECTROENCEPHALOGRAPHIC FINDINGS IN AGED PSYCHIATRIC PATIENTS[1]

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In a previous study (13) evidence was obtained that the electroencephalogram of mentally healthy people changes in old age. The EEG's tended to have slower dominant rhythms and a higher incidence of slow waves when compared to those of young adults. Individual differences, however, were marked, so that some persons over 90 years of age had normal, young adult tracings. In further studies (14, 15) an attempt was made to relate such individual differences to various mental and physical characteristics in old age. There was a tendency for the slower EEG's to be associated with the presence of cardiac and cerebrovascular disease, but little or no relationship to intellectual function could be demonstrated in nonpsychotic subjects. The present investigation extends these observations to aged patients in a mental hospital. The question was asked: How do individual differences in EEG pattern relate to psychiatric diagnosis and prognosis in the aged? Additional findings on the physical status of the patient were studied in relation to both EEG and psychiatric variables.

Most of the EEG work done in gerontology to date has been on institutionalized psychiatric groups. Liberson and Seguin (6) noted a high incidence of slow waves in senile cases where mental confusion and irritability were prominent, and relatively normal EEG's in patients suffering from delusions, anxiety and agitation. Luce and Rothschild (7) reported that 75 per cent of aged cases with organic mental signs had abnormal EEG's, particularly a slow alpha rhythm, whereas only 12 per cent with functional disturbances had abnormalities. Differences between aged patients were also observed by McAdam and McClatchey (9), who found slow activity in the EEG associated with intellectual deterioration, and normal tracings associated with an absence of deterioration. The work of Mundy-Castle and coworkers (12) confirms the high incidence of theta and delta activity in psychoses of senility and points to the diffuse cerebral distribution of such waves. These authors found significant differences between normal old people and psychiatric patients, although a clear EEG differentiation of patients into diagnostic groups was not obtained. Silverman, Busse and Barnes (20) compared the EEG's of psychiatric cases with those of mentally normal individuals in the community, and noted a positive relation between psychologic deterioration and diffuse EEG abnormalities. Focal temporal lobe disturbances, on the other hand, were prevalent even among the normal old subjects and were not related to psychologic impairment.

These studies suggest that the electroencephalogram may be useful in differentiating organic from functional mental disorders in old age. They further suggest that both the frequency of the electric activity and its distribution over the head are importvariables in distinguishing the two types of illness. The present experiment was designed to test the validity of these assumptions. Results on the clinical interpretation and rating of the EEG are presented here. Quantitative measurements, including manual

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and electronic frequency analysis, will be the subject of another report.

METHODS

One hundred and twenty cases were selected from two mental institutions: the Institute of Living, privately operated, and Norwich State Hospital. All consecutive admissions over a 19 month period were studied at the former, with the exception of a few who were too disturbed for testing. Additional subjects from the state hospital were studied as a means of obtaining a more representative sample.

At the outset it was felt that certain types of disorder should be excluded in order to prevent factors from influencing the EEG that are not associated with aging or the usual pathology of senescence. Thus, patients with recent head injury, recent electroshock treatment, history of brain surgery, or present drug or alcohol intoxication were omitted from the sample. Grounds for exclusion also included a history of chronic epilepsy and evidence of neurologic deficit from previous trauma, toxic state, infection, alcoholism or syphilis. Of the original 120 cases, 17 were rejected for these various reasons, although no case was omitted on the basis of EEG findings. The remaining 103 patients, 47 male and 56 female, comprise the sample under study. Their ages range from 65 to 94 years, with a mean age of 75.

Waking electroencephalograms were recorded on an eight channel Grass Model III-D instrument. Fifteen electrodes were employed with both unipolar and bipolar techniques. Occasional mild sensory stimulation insured wakefulness of the subject during the test. Clinical evaluation of the EEG was made by one of us without knowledge of the patient's psychiatric or physical condition. Each patient's psychiatrist was in turn asked to evaluate the psychiatric and physical findings independently of the EEG. Extensive use was made of case histories, data from physical and mental examinations, psychiatric progress notes, laboratory reports on x-rays, electrocardiograms, blood and urine analyses, etc. Diagnostic studies were made in every case within a month of the EEG examination. When questions arose concerning the physical findings, an internist or neurologist was consulted. A total of 30 physicians at the Institute of Living and Norwich State Hospital assisted in this phase of the study.

Medication and history of somatic therapy were carefully recorded for every patient. Except for exclusion of cases with electroshock treatment in the preceeding 6 months, no attempt was made to control these variables. Consequently, 35 were taking some kind of sedative at the time of EEG, 29 were on tranquilizers, 17 on cardiac medication, and several on a variety of miscellaneous drugs. Sedation consisted primarily of barbiturates and chloral hydrate, both of which may produce rhythmic fast activity in the EEG. Statistical treatment of the results, however, failed to reveal any systematic EEG differences between patients receiving sedation and those who were not. Tranquilizers were not subjected to special statistical treatment, since they were taken about equally in the different psychiatric groups. A history of earlier electroshock treatment was present in 16 cases, but the incidence of EEG abnormality in this group was no greater than in the remainder of the sample.

Description of Subjects

Psychiatric Status. The Diagnostic and Statistical Manual of the American Psychiatric Association (23) was used as a basis for classifying subjects. Three groups were formed: (*a*) patients showing unequivocal evidence of brain syndrome, with or without accompanying neurotic, psychotic or behavioral reactions; (*b*) patients showing little or no evidence of brain syndrome, who suffered from various functional illnesses ("disorders of psychogenic origin or without clearly defined physical cause or structural change of

TABLE 1
Description of Sample

Psychiatric Status	No. Cases	Age Range	Mean Age
Functional	45	65–91	72
Doubtful	13	71–89	78
Brain syndrome	45	66–94	77
Total sample	103	65–94	75

the brain"); and (*c*) doubtful, borderline cases who presented an equivocal psychiatric picture. Assignment to the first two groups was solely on the basis of a clear cut presence or absence of brain syndrome. Not all subjects, however, had such well defined symptomatology, thus necessitating the doubtful category. The latter consisted mostly of cases with depressions or delusions who gave the appearance of organic deterioration, but whose symptoms could also be explained on the basis of a severe emotional disturbance and personality disorganization.

Table 1 shows a breakdown of the sample into three diagnostic groups. It should be noted that the two major groups, functional and brain syndrome, both have 45 cases, and that their mean ages differ by 5 years. In comparing the EEG's of these two groups, it is desirable to rule out the effects of age. Subsamples were therefore formed by matching 28 individuals from each category on the basis of age. None of the subjects so matched differed by more than 3 years, and the mean ages of the subsamples were identical.

The definition of brain syndrome used in the present study requires fuller description. It was found that psychiatrists differ widely as to the precise meaning of the term. Extreme cases presented little difficulty, but many patients with mild symptoms were the subject of disagreement. Although this is of little practical consequence for therapy, it could produce variation in research results. To insure a constant rating throughout the sample, the following criteria for brain syndrome were arbitrarily established.

(1) Disorientation in at least one sphere. It may be episodic or appear only as a nocturnal disturbance, but there must be at least several clear cut instances of it.

(2) A definite history of recent memory impairment with defective immediate recall. This may be associated with varying degrees of deficit in remote memory.

(3) Some evidence of intellectual defect, involving disturbances in ability to comprehend language, to perform arithmetic calculations, to furnish information on widely known topics, or properly to use abstract concepts. Evaluation of these abilities was made relative to educational and occupational background.

In addition to the above criteria, which must all be present for a diagnosis of brain syndrome, certain less constant symptoms were used as supporting evidence: marked emotional lability, defects in judgment and deterioration of personal habits.

Patients not fitting this description of brain syndrome were classified as functional or, when the evidence was inconclusive, as doubtful. Besides the gross psychiatric categories already described, further subdivision of the sample was made along diagnostic lines. The brain syndrome group was broken down on the basis of presumed etiology. Fourteen of the 45 patients had a circulatory disturbance, either a cerebral vascular accident or congestive heart failure, that appeared to be a contributing factor to their brain syndromes. The remaining 31 patients were free of obvious circulatory disturbances that might directly affect mental status. No attempt was made to differentiate arteriosclerotic from senile brain disease, since these cannot be distinguished reliably on clinical grounds. All cases of brain syndrome were chronic, although a few with circulatory disturbances had acute confusional states superimposed. The 45 patients with functional disorders were subdivided on the basis of descriptive diagnosis. Affective disorders (usually depression) and paranoid reactions were most prevalent, accounting for 25 and 13 patients, respectively. The remaining 7

were classified as "other," a category that included such miscellaneous diagnoses as psychoneurosis, schizophrenia and adjustment reaction of late life.

Physical Status. The majority of the 103 patients suffered from one or several physical ailments common at this age. For example, clinical evidence of cardiovascular disease was found in 73 per cent of the cases. No attempt was made, however, to restrict the sample in this respect. It was argued that such a limitation would make the results grossly unrepresentative of the average aged patient. Furthermore, the incidence of cardiovascular disease is of interest in itself, especially its relation to EEG and psychiatric diagnosis. A summary of the cardiovascular findings is included in the results below.

Neurologic signs are another frequent finding in this age group, and again no attempt was made to limit the sample on this basis. Parkinsonism occurred in 5 patients, and 9 patients had attacks of syncope or vertigo. Fourteen subjects gave isolated neurologic symptoms, such as a positive Babinski response, extrapyramidal signs or cranial nerve defects, that were not part of a clear cut syndrome or localizable disease process. Among the more common findings were symptoms associated with a cerebral vascular accident. There were 13 such histories, 6 of them recent, and 9 with residual neurologic impairment.

Other physical disorders found in the sample include 4 patients with moderate to severe pulmonary emphysema, and 3 with pulmonary edema associated with congestive heart failure. There were no cases of active tuberculosis. Eight people with diabetes mellitus were adequately controlled by insulin and had normal blood sugars at the time of EEG. Another 4 subjects gave evidence of mild anemia, but none had a hemoglobin level of less than 10 gm. per 100 ml. during the investigation. A mild hyperthyroid condition was present in 1 case. Three patients suffered from nephrosclerosis, but only 1 of these had evidence of uremia with an elevated nonprotein nitrogen level. There were no instances of hepatic disease. Although some of these systemic disorders are known to have a direct influence on the EEG, it is believed that their incidence and severity in the present sample are not sufficient to affect the results appreciably. A probable exception is cardiovascular disease, which is treated statistically in the results that follow.

RESULTS

EEG in Relation to Psychiatric Findings. Electroencephalograms were read according to young adult standards and rated with respect to normality and abnormality. Preliminary observations revealed a high incidence of diffuse slow wave activity (delta and theta). The abnormal records were therefore divided into two categories: a group that showed *diffuse* slow waves between 1 and 7 c.p.s., and a group that did not. Slow waves were considered diffuse if they were bilateral and involved three or four of the major head regions (anterior, posterior, lateral and central). The category with EEG disturbances other than diffuse slow activity was composed of various *mild or focal* abnormalities. Most of the tracings in this group showed either a slow alpha rhythm below 8 c.p.s. or focal slow waves. Focal abnormality was defined as being restricted to one or two of the major head regions, either unilateral or bilateral. A few records with asymmetry, dysrhythmia or excess fast activity were also included in the latter category.

Figure 1 presents the incidence of EEG abnormality in relation to diagnostic group. Whereas the majority of functional cases have normal tracings, the majority of brain syndrome cases have diffuse slow waves. In terms of predicting psychiatric status from EEG, 88 per cent of 32 patients with normal tracings have a functional disorder, and 79 per cent of 38 cases with diffuse slow waves have brain syndrome. Patients with mild or

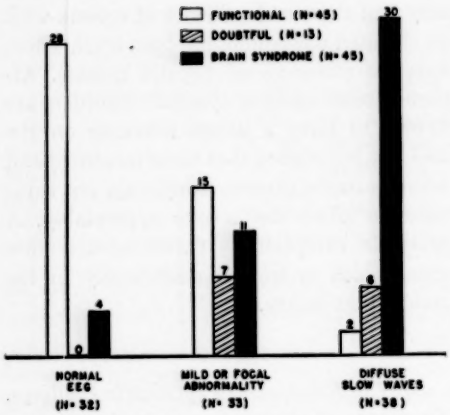

FIG. 1. EEG findings in relation to psychiatric status. Number of cases is given at the top of each bar. $\chi^2 = 51.8$ ($p < .001$).

focal abnormalities fall about equally in the two psychiatric groups. A chi-square test of significance reveals that such findings could occur by chance less than 1 time in 1000. It is interesting that there are no normal EEG's in the doubtful group, which has, instead, about an equal number of mild and diffuse abnormalities.

As noted previously, the brain syndrome and functional groups have a mean age difference of 5 years. In order to rule out the possibility that the above results are due to age differences, a comparison was made between two subsamples of 28 individuals whose ages were matched. The results are presented in Table 2, where it is obvious that the trend observed in the full sample is maintained. Again, the chi-square test is significant at the .001 level of confidence.

Variations in EEG abnormality within the two major diagnostic categories are of special interest to psychiatry. Comparisons were made within the brain syndrome group between patients with circulatory disturbance and those without. No significant trends were apparent, the incidence and type of abnormality being approximately the same for both subgroups. Comparisons between subgroups within the functional category also failed to show striking differences. There was a tendency for patients with affective disorders to have a higher incidence of abnormality than those with paranoid reactions, but this difference was not statistically significant.

Since theta and delta waves are the most common EEG abnormality encountered, an analysis was made of their distribution and localization. Table 3 indicates the number of patients with diffuse, focal and mixed distributions of slow waves. "Mixed" refers to a diffuse disturbance with definite focal accentuation. Both diffuse and mixed distributions are more prevalent in the brain syndrome group, exceeding the functional group by 15 to 1. However, when only focal slow waves with no diffuse involvement are considered, the brain syndrome and functional groups are about equal. Considering slow activity of all types, the incidence among brain syndrome patients is 37 out of 45, while the incidence for functional cases is only 10 out of 45. This difference is significant at the .001 level of confidence.

Localization of focal slow waves is also presented in Table 3. The head was arbitrarily divided into quadrants: left and right anterior and posterior regions. A total of 38 patients had either focal slow waves or a focal accentuation of diffuse slow waves. Approximately three-quarters of these had foci in the anterior quadrants, the remaining quarter in the posterior quadrants. Of the 28 patients with anterior foci, more than half were confined to the anterior temporal area. Another third involved *both* the anterior temporal and frontal areas. Whereas foci confined to the anterior temporal leads

TABLE 2

*EEG Findings on Subsamples Matched for Age**

Psychiatric Status	Normal EEG	Mild or Focal Abnormality	Diffuse Slow Waves
Functional	15	12	1
Brain syndrome	1	5	22
Total cases	16	17	23

* $\chi^2 = 34.3$ ($p < .001$).

occurred about equally in the brain syndrome and functional groups, those that involved the frontal lobe, either alone or in combination with the anterior temporal, were 10 times more common in the brain syndrome group (Table 3).

An interesting finding not shown in the table is the very striking difference between hemispheres with respect to anterior slow waves. Twelve of 28 were unilateral and left sided. There was not a single instance of a unilateral right sided focus. Out of 16 bilateral foci in the anterior region, 11 had a left sided emphasis and 5 were symmetrical. Again, there was no instance of a right sided emphasis. In contrast to these findings, slow waves in the posterior quadrants appeared over each hemisphere in about the same proportion of cases. Another interesting observation is that foci confined to the anterior temporal area tend to be unilateral (10 out of 16), whereas those involving the frontal lobe are usually bilateral (10 out of 12). Figure 2 gives an example of an anterior temporal slow wave focus (see legend for a description of the patient).

EEG abnormalities other than slow waves are listed at the end of Table 3. The incidence of these abnormalities is relatively low, with the exception of a slow alpha rhythm (less than 8 c.p.s.) that occurred in 29 cases—more than a quarter of the total sample. Such slow rhythms were twice as prevalent in the brain syndrome as in the functional group. A similar proportion was obtained for the few cases with bilateral asymmetries in amplitude. Voltage depression refers to a tracing of exceptionally low amplitude, one that has a "washed out" appearance. More brain syndrome than functional patients also showed this type of abnormality. None of the differences between psychiatric groups is statistically significant, however, possibly because of the small number of cases involved. Dysrhythmic activity, defined as marked amplitude surging and frequency instability, was present about equally in the two major diagnostic categories. The same is true for the incidence of excess fast activity, sedative effects taken into account. The only two cases of epileptiform spikes were included in the brain syndrome group, one of these having followed a cerebral vascular accident associated with seizures.

TABLE 3

Incidence and Type of EEG Abnormality in Relation to Psychiatric Status

EEG Abnormality	Psychiatric Status: Functional	Psychiatric Status: Brain syndrome	Psychiatric Status: Doubtful	Total No. Cases
Distribution of Slow Waves				
Focal only	8	7	5	20
Mixed (diffuse and focal)	1	15	2	18
Diffuse only	1	15	4	20
Total slow waves	10	37	11	58
Location of Focal Slow Waves				
Anterior temporal only	6	5	5	16
Both anterior temporal and frontal	1	8	0	9
Frontal only	0	2	1	3
Total anterior*	7	15	6	28
Posterior†	2	7	1	10
Total all areas	9	22	7	38
Other Types of Abnormality‡				
Slow alpha rhythm	8	16	5	29
Amplitude asymmetry	4	8	1	13
Excess fast activity	3	3	0	6
Dysrhythmia	3	3	0	6
Voltage depression	1	4	0	5
Spikes	0	2	0	2

* Sum of all foci involving anterior temporal area, frontal area or both.

† Includes parietal, occipital and posterior temporal areas.

‡ Not mutually exclusive.

EEG in Relation to Cardiovascular Disease. As mentioned earlier, no attempt was made to restrict the number of patients with cardiovascular disease, with the result that there was a very high incidence of such disorders in the sample. Seventy-three per cent of the 103 patients showed clinical evidence of pathology in some part of the cardio-

FIG. 2. Slow wave focus from the left anterior temporal area of an 83 year old man. The patient was classified as "doubtful" psychiatrically because a severe depression made evaluation of brain syndrome questionable. *L*, left; *R*, right; *F*, frontal; *AT*, anterior temporal; *PT*, posterior temporal; *O*, occipital. All leads are referred to an electrode at the vertex.

vascular system. Brain syndrome and functional groups were not significantly different, with 78 and 69 per cent, respectively. The various types of cardiovascular disorder also appeared with greater incidence among brain syndrome patients, but again, differences between groups were quite small. Heart disease was the most frequent finding, occurring in 50 per cent of the total sample. X-ray and physical evidence of generalized arteriosclerosis was found in 40 per cent. Twenty-nine per cent of all cases had calcification of the internal carotid artery, and 3 per cent showed severe peripheral vascular insufficiency. Hypertension (defined as pressures consistently higher than 150 mm. Hg systolic and 90 mm. Hg diastolic) occurred in 37 per cent of the sample, and was the only finding in which the functional group slightly exceeded the brain syndrome group. Two types of circulatory disturbance deserve special attention because of their presumed role in the etiology of brain syndrome, namely, a history of cerebral vascular accident (CVA) and congestive heart failure at the time of examination. Of the 13 patients with CVA's, 10 were in the brain syndrome group as opposed to 1 in the functional group. All 5 cases of congestive heart failure were in the brain syndrome group. These two disorders were the only ones showing appreciable differences between psychiatric categories.

Except for circulatory disturbances that probably affect the brain directly, the relation of EEG to clinical evidence of cardiovascular disease is essentially negative. No significant EEG results were obtained with respect to heart disease or the presence of generalized arteriosclerosis. Table 4 reveals that two-thirds of the 28 subjects with completely negative cardiovascular findings have abnormal EEG's, an incidence comparable to that of the total sample. Patients

TABLE 4

Relation of EEG Findings to Cardiovascular Disease and Hypertension

EEG Findings	Negative Cardiovascular Examination	Cardiovascular Disease	
		Hypertensive	Normotensive
Normal EEG	9	16	7
Mild or focal abnormality	8	14	11
Diffuse slow waves	11	8	19
Total cases	28	38	37

with positive cardiovascular findings also have a high proportion of EEG abnormalities, but among these cases the absence or presence of hypertension appears to be a relevant factor. Whereas hypertensive individuals give twice as many normal as diffuse slow wave patterns, normotensive individuals show a definite trend in the opposite direction. The difference between blood pressure groups is statistically reliable at the .02 level. Patients with cerebral vascular accidents or congestive heart failure have predominantly abnormal EEG's. Only 1 patient with a CVA gave a normal tracing, 7 showed focal slow waves, and 5 diffuse slow waves. Four out of 5 patients with congestive heart failure had diffuse slowing, the remaining 1 having a slow wave focus. Taken together, the incidence of abnormality in these two disorders exceeds expectation for the sample at the .02 level of confidence.

Outcome of Illness. Follow-up studies were made on all patients a year after their EEG. Except for a few long term cases, this time also represents the anniversary of hospital admission. Information was obtained on the outcome of illness, that is, whether the patient had been discharged, remained in the hospital, or had died. A fourth category designated "convalescent" consisted of cases who were still officially enrolled in the hospital, but who had left to visit relatives or reside in a convalescent home. Although social and economic factors are relevant in many instances, the most important determining factor of these various outcomes is the patient's mental and physical progress. *Discharged* would tend to signify improvement in most cases, *convalescent* would indicate somewhat less improvement, whereas *hospitalized* or *deceased* would suggest a stationary or worsening course of the illness. Figure 3 arranges these outcomes in the order of their prognostic significance and relates them to the original psychiatric diagnosis. Three-quarters of the functional group were discharged or in convalescent status at the end of the year. On the other hand, more than two-thirds of the brain syndrome cases had either died or remained in the hospital. These trends are statistically significant at

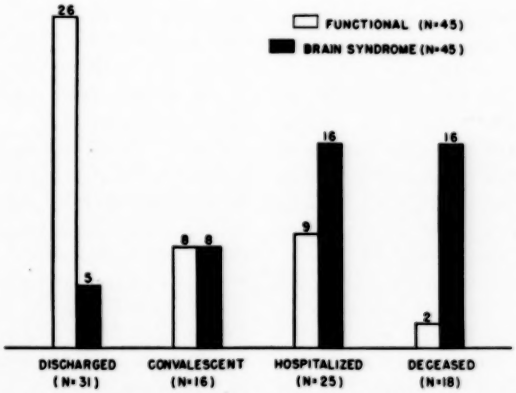

FIG. 3. Outcome of illness after 1 year in relation to psychiatric status. Number of cases is given at the top of each bar. $\chi^2 = 27.1$ ($p. < .001$).

TABLE 5

*Outcome of Illness after 1 Year in Relation to EEG Findings**

Outcome of Illness	Normal EEG	Mild or Focal Abnormality	Diffuse Slow Waves
Discharged	15	14	7
Convalescent	8	6	6
Hospitalized	7	9	12
Deceased	2	4	13
Total cases	32	33	38

* $\chi^2 = 14.7$ ($p < 0.05$).

the .001 level of confidence. When age is held constant by comparison of matched groups, the same highly significant differences are obtained.

EEG is also related to outcome of illness after a year. Table 5 reveals that patients with normal tracings tend to be discharged or convalescent, whereas patients with diffuse slow waves are more likely to remain in the hospital or die. The intermediate category of mild or focal abnormalities show a trend similar to those with normal EEG's, although not as marked. A chi-square test reveals that such findings could occur by chance less than once in 20 times.

Illustrative Cases

Case 1. 91 year old woman with paranoid reaction. The patient is a widow who has been living alone for the past 30 years. During this time she became increasingly suspicious of her neighbors, until 2 years ago she developed frank delusions, thinking that people were plotting to rob and murder her. This was accompanied by occasional auditory hallucinations. She enjoyed good physical health and was quite capable of keeping house for herself. Immediately before hospitalization the paranoid symptoms became worse, culminating in an episode of panic during which she ran into the street screaming.

Physical examination revealed a well preserved elderly woman looking 10 years younger than her stated age. Nutritional status was satisfactory. Cardiovascular studies were essentially negative, except for mild hypertension (180/100) and a slight increase in transverse diameter of the heart. Peripheral arteries showed minimal signs of arteriosclerosis. The only positive neurologic finding was moderate deafness. Blood and urine were completely normal.

Mental examination showed the patient to be oriented in all three spheres. Memory for remote events was considered "good," and for recent events "excellent." She appeared alert, spoke coherently, was well informed, and had no difficulty with tests of abstraction. Her personal habits were described as neat, and she was cooperative to hospital routine. The delusions regarding her neighbors were expressed with considerable conviction, although no new trends or hallucinations were apparent. The patient exhibited much anxiety about the security of her personal possessions. In spite of a mild interest in her surroundings, she generally gave the appearance of sadness and frequently expressed the wish to go home.

A diagnosis of brain syndrome was considered and rejected for lack of clear cut evidence. A final diagnosis of paranoid state was assigned. During the next year the patient remained in the hospital, where she continued to show delusional trends without appreciable insight. Because of her advanced age, and because there was no one to care for her, further hospitalization was considered necessary.

Figure 4 shows a sample of this patient's EEG (upper tracing). There is a well developed alpha rhythm of 9 c.p.s. over the occipital area. In the temporal region, rhythmic 7 to 8 c.p.s. activity is common. Isolated theta waves also appear from the temporal leads, bilaterally. Because of the latter, the record was rated as mildly abnormal according to young adult standards. The significant feature of this EEG, in contrast to the following one, is the preponderance of frequencies in the normal alpha range and the absence of diffuse slow waves.

Case 2. 93 year old woman with chronic brain syndrome. The patient was in good mental health until 6 years ago when, following the death of her husband, she became confused, agitated, delusional and hallucinatory. Her symptoms were especially marked at night, when she was noisy and wandered aimlessly about in a disoriented fashion. The illness progressed until 3 years ago, at which time she was admitted to the hospital in a delirious state.

Physical examination revealed a feeble woman

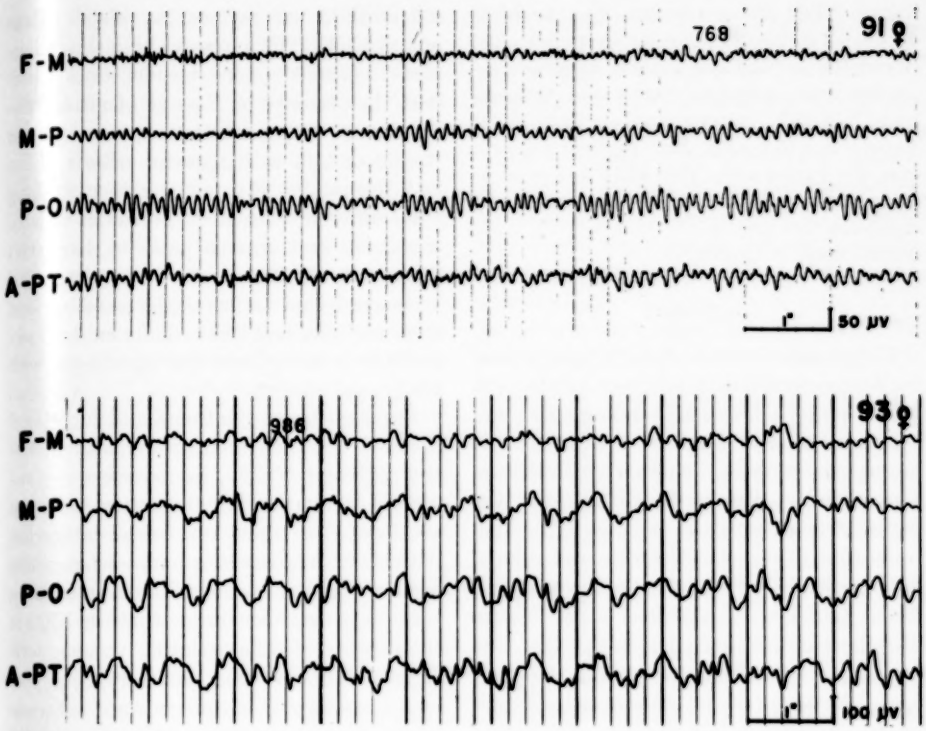

FIG. 4. Top four lines: 91 year old woman with paraniod reaction. Bottom four lines: 93 year old woman with chronic brain syndrome. *F*, frontal; *M*, motor; *P*, parietal; *O*, occipital; *A–PT*, anterior to posterior temporal. Only recordings from the left hemisphere are shown.

of advanced years in fair nutritional status. Evidence of arteriosclerotic heart disease was found, including cardiomegaly, auricular fibrillation and occasional basilar rales; the patient had been taking digitalis for several years before admission. Dyspnea was present with exertion, but there was no dependent edema or angina. She had a blood pressure of 130/90. Both x-ray and physical examination revealed advanced generalized arteriosclerosis; extremities were sometimes cyanotic. A skull film showed calcification of the internal carotid arteries. Neurologic findings were essentially negative, except for a history of syncopeal attacks associated with altered cardiac function. During the course of hospitalization the patient experienced several periods of dependent edema, which responded well to bed rest and medication. At the time of the EEG she had no signs of cardiac decompensation. Blood and urine were within normal limits.

Mental examination showed the patient to be completely disoriented for time and place and partially disoriented for person. Memory was very poor for both recent and remote events. Adequate tests of intellectual function could not be carried out because her speech was irrelevant and incoherent, with frequent perseveration and confabulation. During the interview the patient revealed marked emotional lability. Episodes of resistiveness and assaultiveness made nursing care difficult at times. Personal habits were described as untidy, with occasional incontinence.

The final diagnosis was chronic brain syndrome associated with cerebral arteriosclerosis. A circulatory disturbance due to poor cardiac function was considered a contributing factor. The patient remained in the hospital for 15 months after her EEG, when she died of congestive heart failure.

Figure 4 presents a sample of this patient's

waking EEG (lower tracing). The record is dominated by 2 to 3 c.p.s. delta waves that often exceed 100 μv. The slow activity is diffuse, appearing from occipital, central and temporal leads, bilaterally. Superimposed on these slower waves is a 5 to 6 c.p.s. theta rhythm, seen best over the frontal area. This EEG was rated as severely abnormal with diffuse slow waves. It is significant that there is little or no activity in the normal range of frequencies.

DISCUSSION

The results indicate that within certain limits the electroencephalogram can be used to differentiate functional and organic mental disorders in old age. When the EEG is normal or severely abnormal with diffuse slow activity, correct identification of the psychiatric category is possible in a high proportion of cases. EEG's with mild or focal abnormalities, however, tend to be equivocal. These findings are based on a psychiatric classification set forth by Roth (18). The hypothesis was made that affective and paranoid disorders in old age are distinct nosologic entities independent of cerebral degeneration. Traditionally, psychiatrists have regarded such disorders as part of the symptom picture of senile degenerative disease or its prodromal signs. Without arguing the validity of such a proposition, evidence is presented that affective, paranoid and other functional reactions can be distinguished by EEG from disorders in which mental deterioration is the primary symptom. This differentiation depends upon a strict definition of brain syndrome that utilizes signs of intellectual deficit as the principle criteria. In the present study, patients whose symptoms did not meet these criteria were automatically considered to have a functional disorder, regardless of the nature of their symptoms. It is interesting that Mundy-Castle *et al.* (12) were able to demonstrate a clear relation between incidence of EEG abnormality and severity of senile dementia (based on memory, orientation, organization of thought), but were unable to differentiate the various psychiatric diagnoses by EEG. This suggests that their diagnoses depended upon considerations other than the presence or absence of mental deterioration. Using orientation, memory and stream of talk as diagnostic criteria, Luce and Rothschild (7) found rather striking EEG differences between groups of elderly functional and organic patients. Recently, Barnes *et al.* (2) employed a concept of brain syndrome similar to the one described here, and obtained EEG results on aged patients that are in essential agreement with the present study.

Although brain syndrome and functional disorders are associated with characteristically different EEG's, no trends were observed in relation to diagnostic subgroup within each of these two broad categories. Patients with affective or paranoid reactions had very similar tracings. This is in keeping with the general conclusion that the EEG is not capable of differentiating various nonorganic illnesses (3). Similarly, the presumed etiology of brain syndrome (absence or presence of circulatory disturbance) did not appear to be related to the EEG, which is also consistent with previous observations (17). If serial recordings had been made, it is possible that some of the abnormalities encountered would have been found reversible, especially in patients with more acute manifestations of brain syndrome (4).

Not only are the EEG's in various functional illnesses quite similar; they also tend to be the same as those of normal control subjects. Maggs and Turton (8) have shown that tracings of aged patients with affective disorders do not differ from normal old people. Barnes *et al.* (2) noted that elderly hospitalized patients with functional disorders have slightly fewer abnormalities than a comparable healthy group in the community. These findings are tentatively supported by a comparison of the present sample of functional cases with mentally normal aged subjects in a previous study by one of the authors (13). This group had

practically the same incidence of EEG abnormality as the functional cases described here (around 38 per cent), and most of them showed similarly mild deviations from normal.

The results suggest that diffuse slow wave activity is the most reliable EEG index of mental deterioration. Recently, Weiner and Schuster (22) and McAdam and Robinson (10) reported a correlation between severity of intellectual impairment and amount of slow activity. Quantitative measurements made in the present study tend to confirm this, and will be published at a later date. Although not statistically significant, a slow alpha rhythm was twice as prevalent in the brain syndrome as the functional group, which is consistent with an earlier finding (7). Also as noted previously (20), focal slow waves alone were not related to psychologic deterioration, since they occurred about equally in the two major diagnostic groups. The present investigators were unable to confirm the large amount of fast activity observed by Mengoli (11), or the high percentage of paroxysmal dysrhythmia described by Sheridan *et al.* (19). The latter discrepancy may be due to differences in the definition of "paroxysmal dysrhythmia."

One of the more striking results is the preponderance of slow wave foci from the anterior temporal area, especially their greater occurrence in the left as opposed to the right hemisphere. Because the EEG's were read with knowledge of the previous work of Silverman *et al.* (20), the possibility of a bias toward seeing foci in this region cannot be excluded. An interesting aspect of the findings here is the frequent concomitant occurrence of slow waves in the anterior temporal and frontal areas. Strauss *et al.* (21) have emphasized the susceptibility of the temporal lobes to EEG disturbances resulting from lesions almost any place in the cerebral hemispheres. They note that frontal lesions frequently produce foci that are confined to the temporal area, and state that when both regions are involved electrically, the pathology is more apt to be in the frontal lobe. This suggests that the frontal area may play as great or even a greater role than the temporal area in the production of EEG abnormalities in old age.

The incidence of cardiovascular disease obtained here is higher than that reported by Kay and Roth (5) for aged mental patients. This is probably because less strict criteria were employed in the present study, with many mild or borderline cases included. If the severity of cardiovascular disease had been taken into account, a clearer relation to psychiatric status and EEG might have been obtained. In this connection it is significant that all 5 cases of congestive heart failure and 10 out of 13 patients with a cerebral vascular accident were in the brain syndrome group, and all but 1 of these individuals had abnormal EEG's. The presumption is that such disorders directly affect cerebral hemodynamics to bring about the observed behavioral and electrographic changes.

Although inferences about cerebral circulation based on clinical evidence must be made with extreme caution, it would appear that circulatory disturbances cannot account for all of the EEG abnormalities encountered in the present sample. Twenty-eight subjects had completely negative cardiovascular examinations, and these cases gave as high an incidence of EEG abnormality as those with positive findings. This contradicts previous results on mentally normal old people (15), where significant differences were obtained between individuals with and without clinical signs of cardiovascular disease. It suggests that, in aged psychiatric patients, factors other than disturbances in circulation contribute to the production of EEG abnormalities.

The finding that hypertension is associated with less EEG abnormality than is normal blood pressure must be regarded as very tentative. Most patients designated as hypertensive had only mild elevations of pressure (150 to 200 systolic and 90 to 110 dias-

tolic), and some of these readings probably reflect emotional factors during the examination. Although thorough clinical studies were lacking in many cases, it is believed that only a small proportion of patients had malignant hypertension. No subject showed signs of hypertensive encephalopathy. The results suggest that mild elevations in blood pressure may be a factor in the preservation of normal cerebral potentials, possibly by maintaining adequate blood flow. Further work is needed to clarify this point. It should be noted that Maggs and Turton (8) did not find a relation between EEG and blood pressure in aged patients with affective disorders.

With regard to outcome of illness, the work of Roth (18) has been essentially confirmed. Not only is progress of elderly patients related to psychiatric status, but there is also a tendency for it to be correlated with EEG findings (24). The latter, however, is not of sufficient magnitude to be of great value prognostically in individual cases. It is possible that the EEG may be useful in predicting the outcome of electroshock therapy in the aged, a treatment showing some promise in geriatric psychiatry (16). Preliminary results on 20 cases reveal that patients with diffuse slow activity respond poorly and are likely to develop marked symptoms of confusion.

The present cross-sectional investigation poses many questions concerning the origin and development of EEG abnormalities in old age. One reasonable hypothesis is that a slow alpha rhythm or a focal slow pattern precedes the occurrence of diffuse slow waves, and that in chronic illnesses there is a gradual progression from one type of abnormality to the other. Longitudinal studies on normal old people are now being undertaken by the authors in an attempt to shed light on this hypothesis. Similarly, the relation of EEG to cerebral blood flow and metabolism requires investigation. It is hoped that work currently in progress on this subject may answer some of the questions raised by the EEG findings in cardiovascular disease. A very intriguing problem is the not infrequent observation that severely deteriorated patients may have perfectly normal EEG's, or that psychologically well preserved individuals may have gross abnormalities. A few instances of both types were found in the present study, and similar cases have been reported elsewhere (1). Attempts have already been made to relate the electroencephalogram to underlying neuropathology in the aged (19). Much further research is need in this important area.

SUMMARY

Electroencephalograms were recorded on 103 psychiatric patients between 65 and 94 years of age. Forty-five of these presented clear cut evidence of brain syndrome; another 45 suffered from functional disorders; the remaining 13 had an equivocal psychiatric picture.

A high incidence of diffuse slow wave activity (delta and theta) was found in the brain syndrome group. The functional cases, on the other hand, had a significant number of normal tracings. Uncomplicated focal slowing did not appear to be related to psychiatric diagnosis. Localization of focal abnormalities was predominantly anterior, with more frequent involvement of the left hemisphere.

Nearly all patients with cerebral vascular disease or congestive heart failure showed EEG abnormalities. However, the EEG was not related to generalized arteriosclerosis or to the presence of cardiac disorders that were adequately compensated. There was a tendency for cases of mild hypertension to have normal tracings.

Outcome of illness was related to both psychiatric diagnosis and EEG findings. A significant proportion of patients with brain syndrome and diffuse slow waves remained in the hospital or died within a year. The majority of patients with functional disorders and normal EEG's were discharged or placed on convalescent status.

The above findings are in general agreement with several earlier studies. The implications of this work for geriatric psychiatry are discussed.

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THE EFFECT OF MEPROBAMATE ON THE ELECTROENCEPHALOGRAM[1, 2]

CHARLES E. HENRY, PH.D. AND WALTER D. OBRIST, PH.D.

Although the behavioral changes associated with the use of tranquilizing agents have been extensively described, the neurophysiologic basis of such behavior is as yet poorly understood. Indeed, the failure to find consistent or clearly identifiable effects on such measures as the EEG has been disappointing. This has led to an assumption, based in part on clinical evidence, that such compounds exert their effect on subcortical centers, notably in the region of the diencephalon and the reticular formation. Direct evidence, particularly in man, has been difficult to come by.

Meprobamate (Equanil, Miltown), a derivative of mephenesin, is reported to act upon thalamic and internuncial circuits. We were, therefore, surprised to note that this drug has an easily detectable effect on the EEG. This takes the form of rhythmic fast activity of a type very similar to that characteristically associated with barbiturates. The changes are of some interest to the electroencephalographer, for if not identified, such patterns may be given undue weight in clinical work.

METHODS

Routine clinical EEG's were recorded on 100 hospitalized psychiatric patients receiving meprobamate for therapeutic purposes. Fifty of these patients were taking meprobamate on a chronic daily regime uncomplicated by other medications. The remaining 50 were unavoidably contaminated by a variety of other drugs. The range of dosage varied widely with clinical requirements; no placebos were administered. The effect of a single dose of meprobamate was studied in an additional 15 patients who received the drug during the EEG examination. One or more control records were available for 30 of the total 115 patients.

All recordings were made on a Grass Model III eight channel console, with both scalp-to-scalp and scalp-to-ear combinations derived from our basic 16 lead procedure. The electroencephalographer was usually aware of the medication.

RESULTS

Figures 1 and 2 illustrate the type of fast activity associated with meprobamate. It usually ranges from 20 to 25 per second at approximately 25 μv. amplitude, although records with higher voltages as well as faster frequencies are not uncommon. These rapid waves are rhythmic and well organized and are generally more easily seen in the anterior and central head regions. They are not a "drowsy" pattern.

Table 1 shows the overall incidence of records with fast activity in relation to the chronic maintenance dose of the drug. There is a steady increase in the number of such tracings with increased amounts of medication.

Table 2 gives the distribution of fast activity as rated on a four point scale, using normal physiologic activity as a standard. The cases of no or slight effect tend to be clustered at lower dosage levels, whereas the cases of moderate or pronounced effects tend to be grouped at higher dosage levels. This trend is statistically reliable at the .02 level of confidence.

Because of the inability to establish classical control conditions for patients on chronic meprobamate, we explored the effect

[1] Read before the Annual Meeting of the Society of Biological Psychiatry, Atlantic City, June, 1957. A preliminary report was presented at a meeting of the Eastern Association of Electroencephalographers, Sept. 30, 1956, (5).

[2] Institute of Living, Hartford, Connecticut.

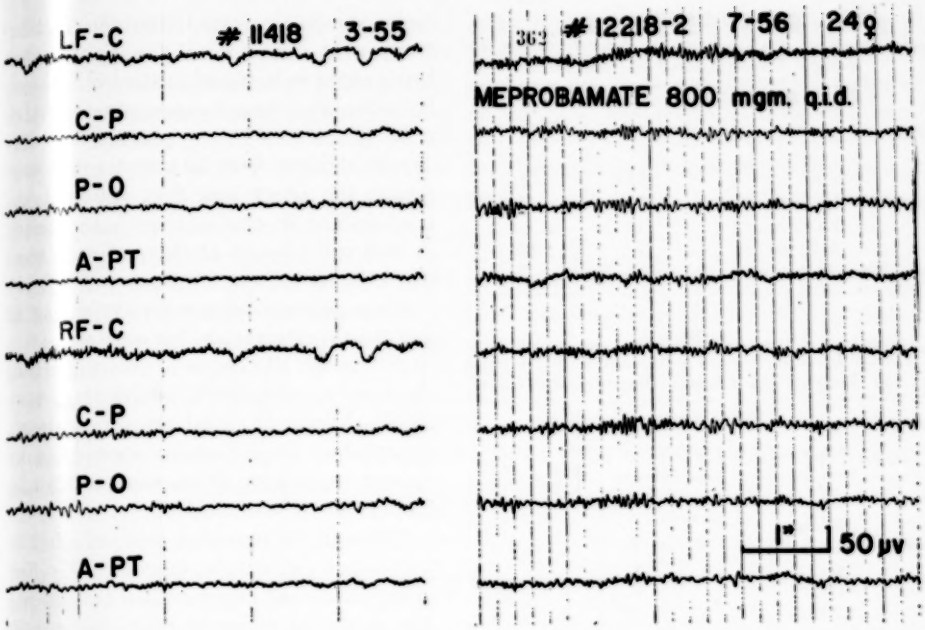

FIG. 1. EEG of a patient not on medication (left), and while on a chronic daily regime of meprobamate (right).

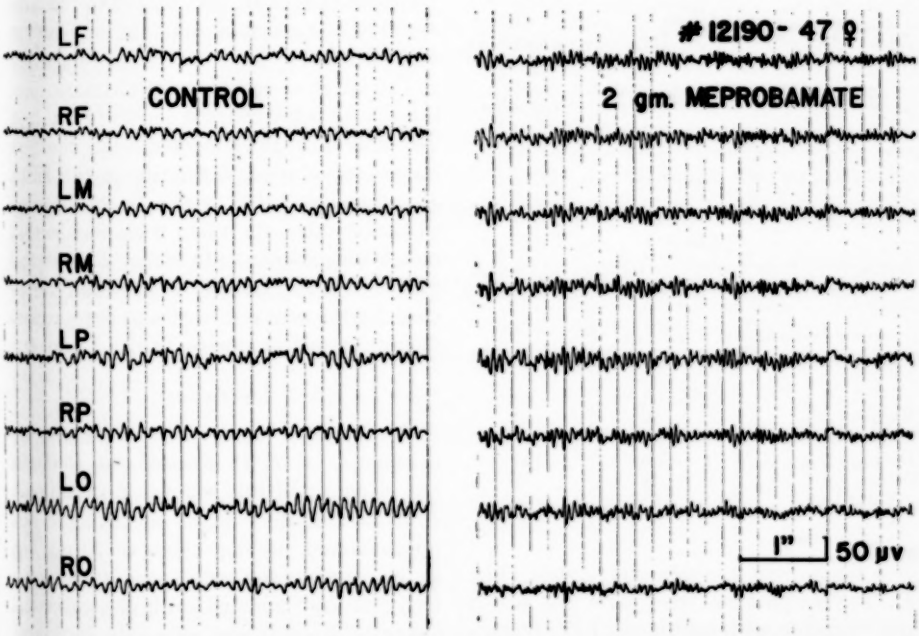

FIG. 2. EEG of a patient before (left) and 1 hour after (right) 2.0 gm. of meprobamate taken orally.

TABLE 1

Incidence of Fast Activity in Patients on Meprobamate Uncomplicated by Other Drugs

Dosage	No. Cases	Cases with Fast Activity
gm.		%
<1.6	7	71
1.6–1.8	17	76
2.0–2.8	11	91
3.2 plus	15	100
Total group	50	86

TABLE 2

Dosage Level in Relation to Amount of Fast Activity 50 Patients on Chronic Meprobamate Only

Dosage	Amount of Fast Activity*			
	None	Slight	Moderate	Pronounced
gm.				
<1.6	2	4	1	0
1.6–1.8	4	8	4	1
2.0–2.8	1	8	1	1
3.2 plus	0	2	8	5

* $\chi^2 = 5.53$ ($p < .02$); based on a 2 x 2 table obtained by combining categories ($d.f. = 1$).

TABLE 3

Acute Effect of 2.0–3.2 gm. Meprobamate by Mouth

Increase in Fast Activity			Total Cases
None	Slight	Moderate	
2	5	5	12

TABLE 4

Incidence of Fast Activity in Patients on Chronic Meprobamate Contaminated by Other Drugs

Source of Contamination	No. Cases	Cases with Fast Activity
		%
Barbiturates	20	80
Chloral hydrate	12	92
Doriden	6	100
Other	12	75
Total group	50	84

of a single dose in acute experiments (Fig. 2). Twelve patients were given 2.0 to 3.2 gm. by mouth with continuous EEG recording. As Table 3 indicates, 10 of these patients showed increased rhythmic fast activity over their control tracing, the shift being slight in half and moderate in the remainder. The changes were observed after only 15 minutes in one patient, but were usually delayed from 30 minutes to 1 hour. Again, the effect was first apparent and best defined in the anterior head regions. It was still present at the end of 2 hours when the record was terminated.

Many patients became drowsy during the prolonged examination, but care was taken to distinguish EEG signs of drowsiness from the more specific effects of the drug. Associated changes in blood pressure were not remarkable. Some patients showed an increased complexity of response to high intensity photic stimulation.

Although the preferred route of administration is by mouth, we examined the effect of intramuscular injection in three patients. The available dilute solution (80 mg. per cc.) limits the amount that may be given. One patient with 800 mg. showed no effect. Two patients with 400 and 800 mg., respectively, showed a minimal increase in fast activity.

The effect of chronic meprobamate combined with other drugs is shown in Table 4. The first three rows include drugs that are known to induce fast activity in the EEG. It will be noted that even with the addition of barbiturates, the effect is similar to that seen with meprobamate alone. The overall incidence of fast activity is essentially identical for the contaminated and pure experimental groups (*compare* Tables 1 and 4).

DISCUSSION

The original reports by Berger and his colleagues (1, 2, 4) stressed the thalamic site of action of this compound in animals, with an inhibitory effect on thalamic and interneuronal circuits. Doses of 20 mg./kg. in the cat synchronized the spontaneous activity of the thalamus, with electrocortical changes (slowing) seen only with very large doses.

The first report dealing with increased fast activity in man from meprobamate appears to be that of Miletto *et al.* (6), who describe a generalized fast pattern resembling a barbiturate effect. Our independently conceived study is in agreement. The paper by Glotfelty and Wilson (3) specifically mentions a search for fast activity in frontal and temporal regions, none being found. The recent study by Tucker and Wilensky (7) reports definite fast activity in 56 per cent of their schizophrenic patients.

In our experience this pattern is clearly discernible in the majority of cases. We have a smaller series from a general hospital population showing the same changes. On several occasions involving diagnostic EEG workup on patients allegedly without medication, a pronounced and unexpected fast rhythm was seen. Further investigation disclosed that the patient was taking meprobamate, at times self-administered. This is, of course, a serious complicating factor in clinical EEG work; our laboratory now makes special inquiry regarding all tranquilizing agents.

SUMMARY AND CONCLUSIONS

We have repeatedly noted a clear increase in rhythmic fast activity in patients on meprobamate, the changes being more pronounced with higher doses of the drug. Fifty uncomplicated cases showed excess fast activity in 86 per cent of the EEG's. Another group of 50 cases contaminated by other drugs had an incidence of 84 per cent. Ten out of 12 cases receiving a single acute dose by mouth showed increased fast activity. This effect, which resembles that seen with barbiturates, thus represents an important variable in clinical electroencephalography.

Acknowledgments. We wish to thank Mrs. Phyllis Porter and Miss Rosa Anglas for the EEG recordings, and Dr. William Zeller for assistance in arranging the clinical schedules.

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THE EFFECTS OF TWO ANTISEROTONIN SUBSTANCES (BAS AND BAB) AND OF BUFOTENIN ON THE SPONTANEOUS ELECTRIC ACTIVITY OF THE BRAIN[1]

FRANCO RINALDI, M.D.[2]

BAS, or benzyl analog of serotonin (1-benzyl-2,5-dimethylserotonin), is a substance possessing marked antiserotonin properties *in vitro* and *in vivo* (23). BAS has been administered to human patients as an antihypertensive agent by Wilkins and Hollander (26). These authors report that a frequent side effect of BAS is marked sedation or tranquilization; the patients feel relaxed and are often sleepy. Rudy and collaborators (19) have tested the action of BAS as a tranquilizer in chronic psychotic patients. It is in association with this study that the effect of BAS on the EEG of human subjects and on the electric activity of the brain of rabbits has been investigated.

BAB, or benzyl analog of bufotenin (1-benzyl-2,5-dimethylbufotenin), is another powerful antiserotonin agent (24) which has also been tested clinically for hypotensive action by Wilkins and Hollander (quoted by Shaw and Woolley). BAB, kindly supplied by Dr. D. W. Woolley, has also been studied as to its effects on the electric activity of the brain in rabbits. A similar investigation has been conducted using bufotenin, the substance from which BAB is derived, and which is reported to be hallucinogenic (6).

METHODS

Studies in Rabbits. The experiments were made on adult albino rabbits, unanesthetized, noncurarized and adequately restrained to immobilize the head for the implantation and fixation to the skull of brain electrodes. Stainless steel electrodes were used and, for their placement in subcortical structures, the stereotaxic planes of reference of Sawyer and collaborators (20) were followed. The recording was done by means of an eight channel Grass electroencephalograph.

All substances were administered intravenously. BAS was injected as a solution containing 2 mg. per cc. prepared by Squibb and Sons, in amounts of 2 mg. per kg. each injection, repeated at intervals of not less than 15 minutes until the total dosage reported below with the results was reached. BAB was administered in the same way but employing a 10 mg. per cc. solution in distilled water. Bufotenin monooxalate was given as a solution of 1 mg. per cc. in amounts of 300 μg. per kg. for each injection.

Studies in Man. Electroencephalographic examinations were done in 15 chronic schizophrenic patients during treatment with BAS and also off treatment. The patients belonged to the group studied by Rudy and collaborators (19). The EEG recording was done in the routine fashion employed for diagnostic purposes. The patients were given BAS orally, and when each was receiving the maximum daily dosage which varied from 50 mg. q.i.d. to 100 mg. q.i.d., the electroencephalogram was recorded.

During BAS treatment most of the patients were quiet and cooperative enough to permit an electroencephalographic record to be made without the use of a sedative, but when off treatment many of our subjects had to be sedated (secobarbital, 1½ to 3 gr. orally or 1½ gr. i.m.) before a satisfactory electroencephalographic record could be obtained. Since the use of secobarbital

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for the control record alone might invalidate the comparison between such records and those with BAS alone, three series of records were made: one control series without BAS and with or without secobarbital, as found necessary, a second series during treatment with BAS alone, and a third one with BAS plus secobarbital.

RESULTS

Spontaneous Electric Activity of the Normal Rabbit Brain. Some of the electric phenomena observed under the influence of the experimental drugs are not diffuse alterations but changes limited to certain structures. Therefore, it is necessary to illustrate first the electrographic patterns commonly recorded from the nervous centers in question under control conditions (mechanically restrained, unanesthetized animals).

In Figure 1 an example of such a normal pattern is given; at the beginning of the record is shown a synchronized pattern usually termed "sleeping." In the motor cortex, slow waves and 14 c.p.s. spindles predominate, while in the visual cortex high voltage (200 to 300 μv.) slow waves are present; in the hippocampus large amplitude (200 to 300 μv.) slow waves with fast "riding" frequencies of smaller voltage; in the subcortical structures, amygdala, putamen, and reticular formation of the midbrain, the recorded activity is of low voltage (20 to 50 μv.) and predominantly fast (bands 16 to 18, 22 to 24, and 30 to 32) as represented in Figure 1. At the arrow the animal was touched lightly and an "alerting" reaction

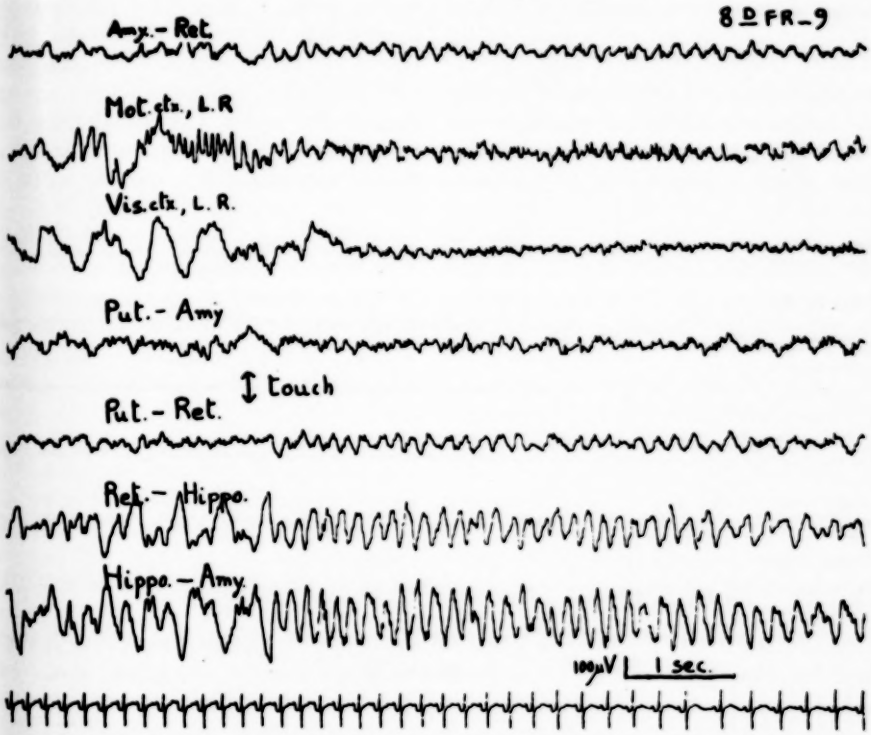

FIG. 1. Control record of the electric activity of various structures of the rabbit brain. Bipolar recording in series. Leads as indicated. The bottom tracing is an ECG lead.

(Key to the abbreviations in all figures: Amy., amygdaloid nucleus; Ret., lateral reticular substance of the midbrain tegmentum; Mot. ctx., motor cortex; Vis. ctx., visual cortex; Put., putamen; Hippo., hippocampus; Sep., septum; R., right; L., left; ECG, electrocardiogram.)

occurred with the appearance of the "alert" or desynchronized pattern. The chief characteristics of electrographic alertness are: (*a*) suppression of the high amplitude slow waves and 14 c.p.s. spindles in the cortical leads and appearance of low voltage fast frequencies; (*b*) substitution of the random slow waves of the hippocampus with a regular 5 to 7 c.p.s. rhythm (hippocampal theta rhythm of Arduini and Green); (*c*) little change in the rhythm of other subcortical centers consisting in some intensification of the fast activities and appearance of 5 to 7 c.p.s. waves synchronous with those in the hippocampus. In bipolar recording the amplitude of these waves seems to be related to the orientation of the electrodes in the field of the hippocampal generator.

Effects of BAS on the Electrographic Activity of Rabbit Brain. Amounts of BAS up to 6 mg. per kg. do not affect significantly the above described picture or alter the relative proportions and alternation of sleeping and alert periods. Additional administration of BAS introduces a typical electrographic picture which is fully developed after dose levels of 10 to 14 mg. per kg. have been reached.

In Figure 2, three strips of record are presented. The left one illustrates the control pattern of sleep; the right one, a control pattern of alertness; the central strip shows the effect of 10 mg. per kg. of BAS. All leads except those from the hippocampus show an activity similar to that seen normally in the EEG alert periods. This is a change which takes place gradually with increasing dosage and finally becomes permanent. In the hippocampus the normal patterns have undergone a profound disorganization: the regular, well synchronized 5 to 7 c.p.s. rhythm, which is to be expected simultaneously with "alertness" in the cortical record, ceases to be the chief characteristic. Instead the hippocampus shows a random mixture of slow waves, some 5 to 7 c.p.s. rhythm, and pointed high voltage waves accompanied by bursts of faster "spikes." The two latter convulsive-like phenomena project now and then to the cortex. Occasionally the high voltage pointed waves appear in groups of 4 to 5 elements with amplitude up to 500

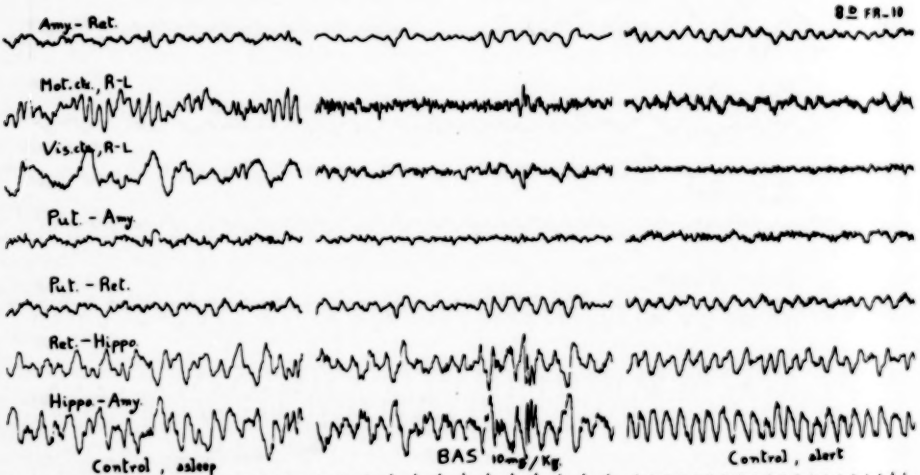

FIG. 2. Effect of BAS (10 mg./kg.) in the rabbit; middle record. The record to the left is an example of the normal "sleeping" pattern and the record to the right shows the normal "alert" pattern.

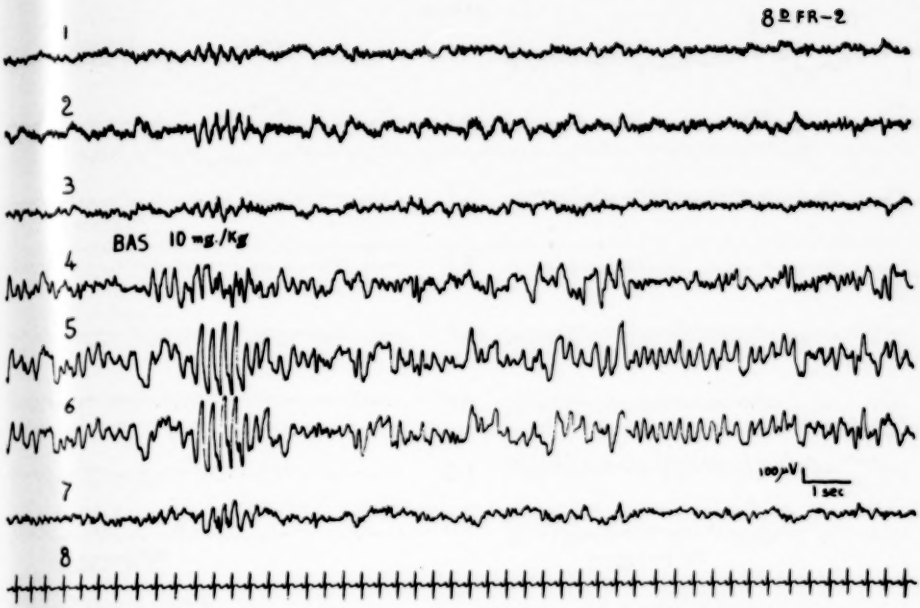

FIG. 3. Effect of BAS (10 mg./kg.) in the rabbit. The leads are: (*1*) left motor cortex; (*2*) right motor cortex; (*3*) right-left caudate nuclei (bipolar); (*4*) right-left limbic cortex (bipolar); (*5*) right hippocampus; (*6*) left hippocampus; (*7*) right-left anterior thalamic nuclei; (*8*) ECG.

μv. (Fig. 3). Such paroxysmal discharges may occur frequently, especially after the administration of larger amounts of BAS. But a fully convulsive pattern is never seen to develop, nor do convulsive movements or other phenomena accompany or follow these hippocampal discharges. The largest amounts of BAS administered were 24 mg. per kg.

The drug has a definite effect on the heart: moderate amounts (up to 6 mg. per kg.) produce bradycardia; larger doses change the shape of the ECG altering the T wave and the origin of the S–T segment. These ECG changes are especially evident during the first few seconds immediately following each intravenous additional dose. After 15 mg. per kg. alterations of the ECG become more severe and long lasting.

Effect of BAS on the Electroencephalogram of Psychotic Patients. In 12 out of the 15 patients examined, no noticeable modification of the EEG appeared during treatment; this is equally true of both the waking and sleeping EEG records. It was noticed that while on BAS the patients were generally more quiet and cooperative and would fall asleep during the test without the use of other sedatives.

In three patients only was a change in the EEG noted. The control record of these subjects showed a dominant alpha rhythm of fairly large amplitude and markedly responsive to the Berger arrest reaction on opening the eyes. During BAS treatment the amplitude of the alpha rhythm was greatly diminished with irregularity of shape and tendency toward slowing. This is shown in Figure 4 in the BAS record; at closure of the eyes a clear increase in voltage of the fundamental activity fails to develop. Such changes induced by BAS did not seem to appear in all subjects with a dominant alpha in the control record; for 2 of the 12

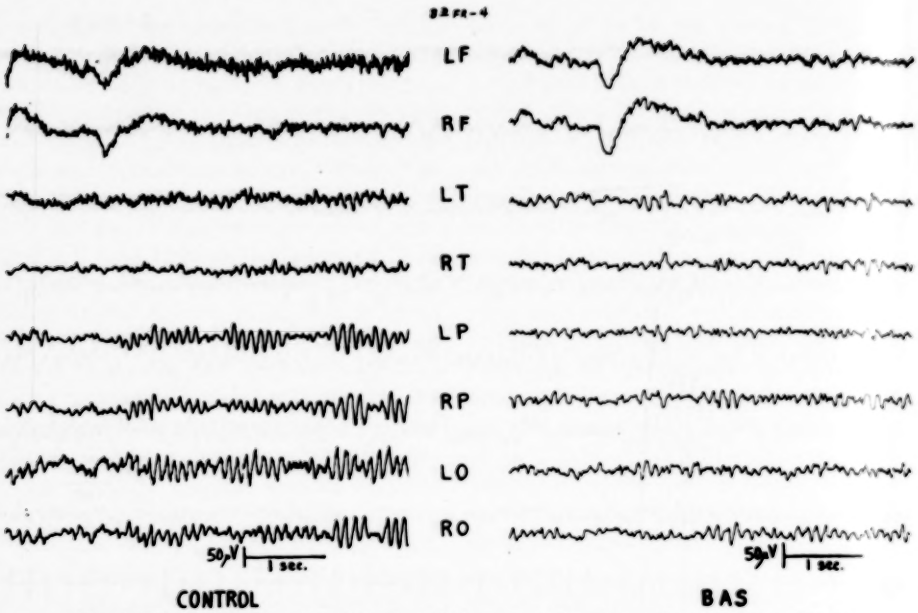

FIG. 4. Effect of BAS on the electroencephalogram of chronic psychotic patients. The left record was taken before treatment with BAS; the right record was made when the patient was receiving daily 300 mg. of BAS orally.

patients who showed no EEG changes under BAS had control EEG's of the dominant alpha type.

Effects of Bufotenin on the Spontaneous Electric Activity of Rabbit Brain. The intravenous administration of 300 μg. per kg. of bufotenin in the rabbit is immediately followed by a series of physiologic phenomena all related to intense stimulation of smooth musculature of various body systems: emission of intestinal gas and defecation; wheezing respiration from bronchoconstriction; vasoconstriction denoted by the pallor, but not cyanosis, of the pinna of the ear, with obvious narrowing of all visible blood vessels. The injection of bufotenin has an immediate effect on the heart; a heart arrest develops in 0.5 to 1.0 second and lasts 1 to 3 seconds, and is probably produced by a vagal reflex because it is entirely prevented by atropine. Within a period of 1 to 2 minutes after the injection these signs disappear and the heart resumes a regular rhythm obviously bradycardiac. Examination of the electric cerebral activity following the injection of bufotenin (0.3 to 3 mg./kg. total dosage), and for long periods (1 hour) after the peripheral effects have subsided, reveals an enduring change. The slow waves and the 14 c.p.s. spindles of the sleeping pattern disappear permanently (Fig. 5, left strip). All leads show an activity apparently identical with those of an alert record. The hippocampal theta rhythm, in the absence of alerting stimulation, is of low voltage and at the lower limit of its usual frequency range (5 to 7 c.p.s.). Nevertheless, an alerting stimulus can still induce a noticeable change. In Figure 5 is shown the effect of barely touching the animal. The alerting effect exerted on an activity already desynchronized by bufotenin results in a paradoxical generalized increase of voltage. This involves the cortical fast activity and, more dramatically, the hippocampal theta rhythm which doubles its amplitude and accelerates to a frequency of 7 c.p.s.

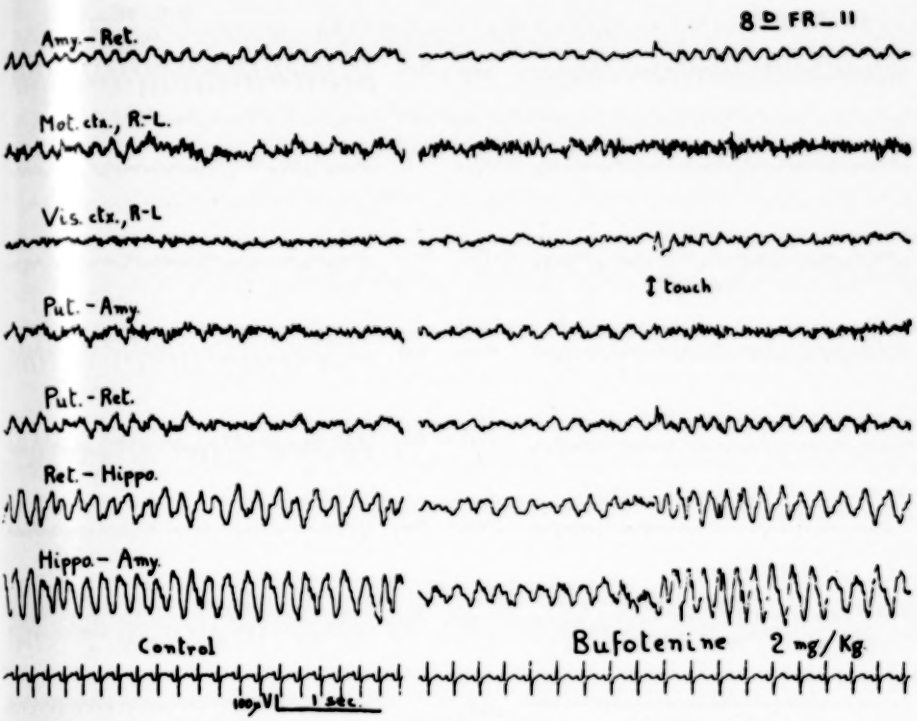

FIG. 5. Effect of bufotenin (2 mg./kg.) in the rabbit (right record)

Effects of BAB on the Spontaneous Electric Activity of Rabbit Brain. The administration of BAB in amounts up to 6 mg. per kg. produces a long lasting suppression of the slow waves and 14 c.p.s. spindles characteristic of the "sleeping" record. Thus the resulting general pattern is undistinguishable from that of "alert" control records. Larger amounts of BAB intensify the alert picture mainly because of the increase in voltage of the hippocampal theta rhythm which, however, remains of normal type as to frequency and wave form. Furthermore, a novel phenomenon appears in the leads from the putamen: fast frequencies on three bands, 20, 32 to 34, and 45 to 50 c.p.s., with an amplitude of 100 to 200 μv. (Fig. 6). These fast frequencies show further increase in amplitude with additional administration of BAB (Fig. 7) but remain localized to the putamen. The amplitude of these fast frequencies is inversely proportional to the distance of the recording tip of an exploring electrode from the putaminal gray. The drop in voltage is more pronounced when the electrode is placed in structures dorsal or dorsomedial (caudate nucleus) or ventral (amygdaloid nucleus) to the putamen. The decrease is more gradual if one records from points medial to the putamen; the amplitude remains considerable in recordings from the globus pallidus. With the largest doses of BAB administered (20 to 25 mg. per kg.), some slow activity reappears in the cortical leads, which respond normally to alerting stimuli (Fig. 7, lower record: cortical desynchronization after painful stimulation). The lower record of Figure 7 also illustrates the effect of an alerting stimulus upon the fast putaminal activity; the frequency drops for 1 to 2 seconds from an average of about 30 to 35 c.p.s. to about 18

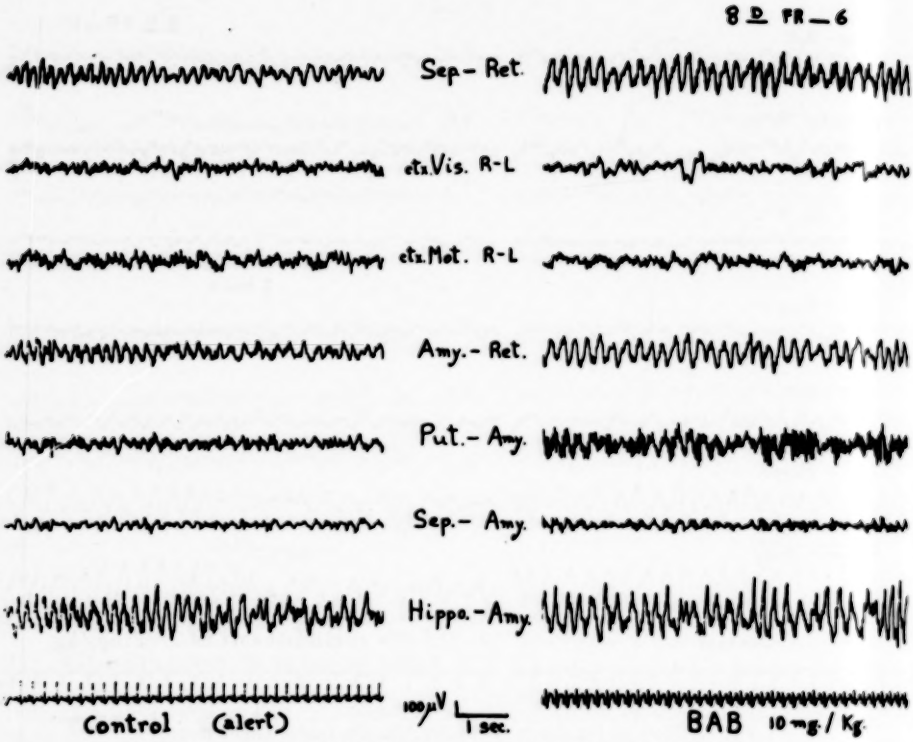

FIG. 6. Effect of BAB (10 mg./kg.) in the rabbit (right record)

to 22 c.p.s. This fast activity of unusually large amplitude seems to remain localized to the region of the lenticular nucleus with its center in the putamen. It would therefore be impossible even to suspect its presence by examining tracings from the cortex alone or to detect it from nearby structures such as the amygdala. In the cortex and elsewhere fast frequencies occur but never of larger amplitude than under control conditions.

Neither BAS nor bufotenin ever induced large voltage fast frequency activity in the putamen. By administering BAB after BAS or bufotenin a similar change in the waves of the putamen can be induced with amounts of BAB of the same magnitude as without pretreatment with the other drugs. The effect of BAB (10 mg. per kg.) in an animal pretreated with bufotenin is shown in Figure 8.

DISCUSSION

Effects of BAS in the Rabbit. Apart from a general effect of suppressing the characteristics of the "synchronized" pattern of sleep and introducing an "alert" pattern, BAS alters the activity of the hippocampus. The BAS induced type of hippocampal activity has features suggestive of a convulsive nature. Any convulsive-like phenomena observed in the hippocampus must be cautiously interpreted because of the great irritability and low threshold of that structure. It is not uncommon that the simple introduction of an electrode in the hippocampus starts convulsive discharges (10). It is, therefore, not unlikely that after the initial irritation has subsided, the mere presence of the electrode creates a site of very low threshold ready to discharge paroxysmally.

Thus it is difficult to asses whether the

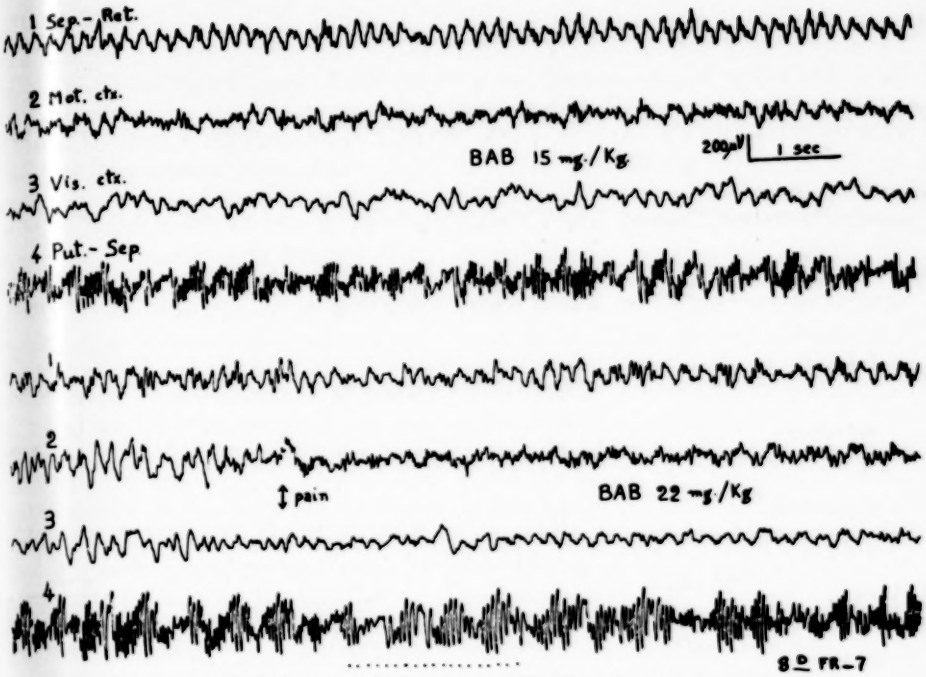

FIG. 7. Effect of BAB in the rabbit. The upper four-tracing record was taken after 15 mg./kg. had been injected. The lower record with leads matching the four upper ones was obtained after injection of 22 mg./kg. of BAB.

convulsive-like discharges induced by BAS are the expression of a specific effect of the drug upon that structure or whether they are the first sign of an unspecific convulsive action appearing at the most irritable site.

However, the peculiar character of certain BAS induced hippocampal discharges, namely the synchronous bursts of high voltage waves, are very dissimilar from the spike discharges usually seen in the hippocampus as a result of mechanical irritation or electric stimulation. Furthermore, apart from the convulsive-like components, the hippocampal pattern is basically disorganized by the presence of random slow waves. Such slow waves would be considered normal if the cortical record were at the same time exhibiting a "synchronized" pattern of sleep. But this is not the case; the hippocampal slow activity is present while the cortex presents an alert picture. This does not lead to the conclusion that we are dealing with a dissociation between neocortical and paleocortical "alertness." The convulsive discharges show that the hippocampal activity is not simply the one normally seen during sleep, but is fundamentally abnormal. Thus we may say that BAS has an effect on the electric activity of the brain and that it alters, perhaps in a convulsive manner, the activity of the hippocampus more than that of other structures.

In more than one respect many effects of BAS resemble those of reserpine (26). As to the electric activity of the brain, it is perhaps significant that reserpine, like BAS, induces in experimental animals an "alert" cortical activity (Carreras and Angeleri, Monnier and Gangloff, Rinaldi and Himwich (16), and Terzian, in rabbits; MacLean in acute cats; Killam and collaborators in chronic cats). Furthermore, reserpine too enhances the irritability of the hippocampus and sometimes produces spontane-

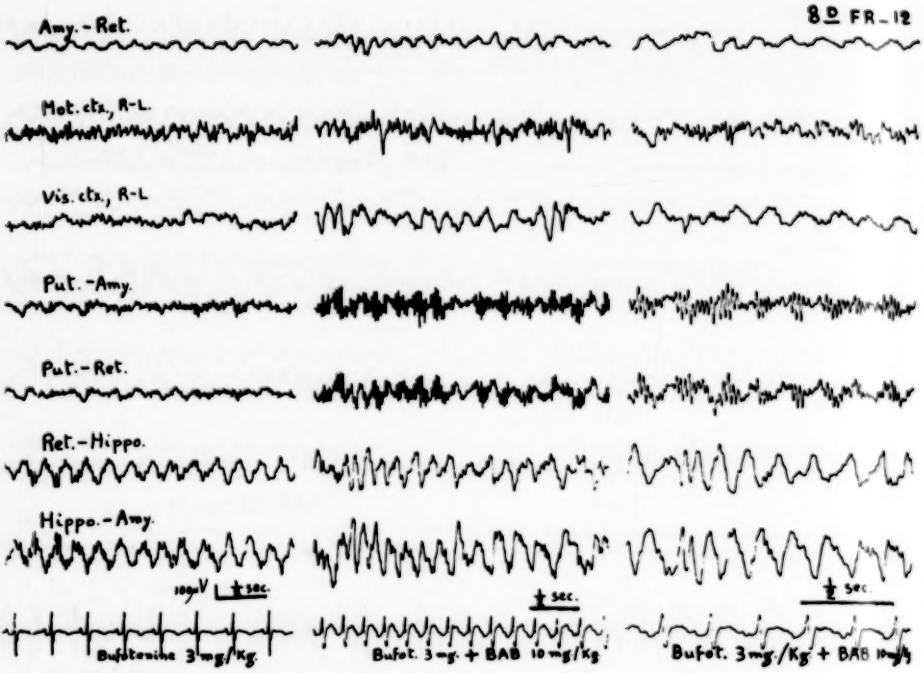

FIG. 8. Effect of BAB after bufotenin in the rabbit. Left record: effect of bufotenin (3 mg./kg.). Middle and right records: after BAB (10 mg./kg.) had been injected in the same animal; in the right record, the time axis is of double length.

ous hippocampal convulsive activity (7, 9, 22). From a more general point of view one may raise the question of the relationship that such rhinencephalic functional changes have to the tranquilizing effects of both reserpine and BAS. In the same respect, what is the significance of the convulsive effect exerted by chlorpromazine (14) upon another rhinencephalic structure, the amygdala? Is a limbic system seizure state equivalent to a functional ablation of that system, as MacLean suggests? These questions are very enticing but no answer can be given on the basis of the facts available at present.

Effect of BAS on the EEG of Psychotic Patients. Because of the small series of patients examined, one can stress only that BAS in the amounts used does not affect the EEG in the majority of patients. As to the depression of the voltage of the alpha rhythm occurring in only three subjects, it is the opinion of the author that further studies are necessary, mainly in patients with control EEG's of the dominant alpha type before an interpretation can be attempted.

Effect of Bufotenin on the Spontaneous Activity of Rabbit Brain. The enduring "alert" pattern induced by bufotenin is an effect which is seen with other hallucinogenic agents such as LSD and mescaline (5, 8, 17). The nature of such drug induced electrographic "alertness" is a question requiring more detailed study—particularly the hypothesis that such activation is due to an excitation of the reticular activating system should be subjected to critical reexamination. Figure 4 illustrates that an alerting stimulus can induce a further change in the activity already desynchronized by bufotenin. An easy and simple explanation would be to invoke degrees of stimulation of the activating system. We

may accord bufotenin a degree of stimulation sufficient to suppress the slow waves of "sleep." Then a higher degree of stimulation is produced by the sensory stimulus. Thus the features of EEG alertness, especially the hippocampal theta rhythm, are reinforced, generating the voltage increase. But one cannot avoid wondering whether it is right to invoke a stimulation effect, direct or indirect, on the activating system whenever one finds a drug induced alert pattern. The inconsistencies between behavioral effects and those of the electric brain activity are the main stumbling block of the hypothesis that correlates the cortical electrographic picture with the functional state of the activating system and with behavior. Bufotenin, which produces excited behavior in animals, "alerts" the cortical electric activity as does reserpine, a tranquilizer. The EEG reaction that follows a peripheral alerting stimulus in the bufoteninized animal (Fig. 4) produces exactly the same EEG pattern as before bufotenin (Fig. 1). The only difference is that with bufotenin the tracing preceding the stimulus lacks the slow waves of the "sleeping" record. It could very well be that the suppression of the slow waves by bufotenin is an action entirely independent of the state of function of the activating system which still can exert its typical effect.

Perhaps the suppression of the slow waves with the production of a "desynchronized" telencephalic electric activity by hallucinogens is due to an effect at the telencephalic level. It may be related to the inhibition of cortical synapses demonstrated by Marrazzi to be a common property of such drugs. As Purpura suggests, it may be the inhibition of axodendritic cortical activity which is the substratum of the desynchronization.

In any case it seems logical to agree with Killam and collaborators in their statement that "the various pathways directly involved in, and exerting tonic influence upon, the EEG activation pattern and behavioral arousal must be reinvestigated. Pharmacological agents will be an important tool."

Effects of BAB on the Spontaneous Electric Activity of Rabbit Brain. The appearance of fast activity of considerable voltage limited to the nucleus lenticularis and especially to the putamen is a unique phenomenon. Of the three tryptamine derivatives here considered, only BAB was able to evoke it. Thus one can consider this action specific for BAB, at least until other substances are found to produce the same effect.

The nature of this putaminal fast activity has yet to be determined. It is not clear whether it should be interpreted as a localized convulsive manifestation. It does not appear *ex abrupto* but builds up as a magnification of those low amplitude fast activities normally recorded from the region of the basal ganglia. By lengthening the time axis (Fig. 8, right), it can be shown that the rhythm is smoothly sinusodial with waning and waxing of amplitude similar to the "beating" or "modulation" of truly periodic phenomena such as the alpha waves of the human EEG. It never spreads and never gives way to frankly convulsive patterns either localized or spreading. Most probably such a prominent but localized fast activity is the result of synchronization of the cell population of the nucleus lenticularis with maintenance of the normal pacemaking rhythm: thus results the increase in voltage with unchanged frequency. The fast rhythms seen normally in the cortex and the caudate nucleus do not show a similar increase in voltage after BAB. This fact can be taken as evidence that they are of different origin and are independent of the activity of the nucleus lenticularis. Again cortex and putamen activity seem to behave quite differently, in fact in an opposite manner, in response to an alerting stimulus (Fig. 8).

The decelerating effect of an alerting stimulus upon the BAB induced putamen fast activity may serve also as a differentiating characteristic in respect to the low voltage fast frequencies produced by volatile anesthetics and those which appear, chiefly in the cortex and in the caudate, in light barbiturate anesthesia (2, 21). Such fast waves induced by anesthetic agents at a certain stage of their action are reinforced and accelerated by alerting (17, 18).

As a final consideration one must point out that the effects of BAS and those of BAB are entirely different. The only one common to both is the tendency to suppress enduringly the "sleeping" cortical patterns; but this change cannot be considered characteristic or indicative of a common mechanism of action, as has been indicated above in the discussion of bufotenin.

BAS and BAB both possess antiserotonin properties. BAS was studied first and the alterations produced by that drug in the electric activity of the hippocampus were observed and thought to be significant because the hippocampus has a relatively high serotonin content, at least in man (4). Then BAB was studied with entirely different results. It is true that the lenticular nucleus also has a notable concentration of serotonin. But why, then, do the two substances not have comparable effects on both structures? Thus it seems that the data reported give no clues as to whether or not the change in the electric activity of the brain is due to their antiserotonin action.

SUMMARY

1. BAS (benzyldimethylserotonin) induces convulsive-like nonspreading electric discharges in the hippocampus of the rabbit.

2. BAB (benzyldimethylbufotenin) produces continuous fast activity localized to the lenticular nucleus, chiefly in the putamen. The amplitude is three to four times larger than that of waves of comparable frequency normally present in the lenticular nucleus and in other parts of the rabbit brain.

3. Bufotenin (*N*,*N*-dimethylserotonin) causes the disappearance of slow wave high voltage activity and introduces an enduring "alert" desynchronized pattern.

4. The electroencephalogram in 12 to 15 chronic psychotic patients did not show significant changes under treatment with BAS. In three subjects only, however, a decrease of the amplitude and slowing of the fundamental alpha activity were observed.

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CLINICAL EVALUATION OF BAS (BENZYL ANALOG OF SEROTONIN): A TRANQUILIZING DRUG[1]

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The drug BAS, the benzyl analog of serotonin, has had only one previous clinical trial, that of Wilkins and Hollander (6) on patients with hypertension. In the course of this exploratory study they noted a state of sedation and tranquilization which was so definite that it tended to limit the dosage of BAS. One thought that prompted this investigation was that such a side effect in the treatment of hypertension might be desirable in the management of disturbed, hyperactive, psychotic patients. In addition to this practical suggestion, there was a second of theoretical importance for the present clinical investigation from the work of Shaw and Woolley (4), who have synthesized BAS to counteract the actions of serotonin in the body. Because serotonin is a smooth muscle constrictor, it has received consideration as a possible factor in the production of hypertension, and Wilkins and Hollander (6) found it effective in reducing the blood pressure in about 25 per cent of patients with essential hypertension (2). But the hypothesis of Woolley and Shaw (7) indicates that disturbances of serotonin may also play a part in mental disease. The formulas of serotonin, BAS (1-benzyl-2,5-dimethylserotonin), and reserpine reveal that they all contain the indole nucleus (Fig. 1). The present viewpoint suggests that the two drugs prevent the action of the hormone serotonin by displacing it from its receptor sites, whether in the brain or in other parts of the body. In broad outline, this was the status of BAS at the time we undertook to test its efficacy in the treatment of schizophrenic patients.

[1] Read before the Annual Meeting of the Society of Biological Psychiatry, Atlantic City, June, 1957.

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METHOD

For this study 24 moderately disturbed, chronic psychotic female patients were chosen. These patients were well known to the investigators as they had been the subjects of previous researches on the effects of tranquilizing drugs over a period of 3 years. This was a great advantage since the characteristic psychopathologic picture of each patient was well known, including spontaneous variations and the alterations evoked by previously administered tranquilizing agents. All of our patients were of middle age or advanced years and had been hospitalized for an average of 18 years. Sixteen were classified as chronic paranoid schizophrenics, seven as hebephrenic schizophrenics, and one as schizoaffective. Because this drug is so new and we were not sure of the dosage necessary to induce tranquilization and yet avoid undesirable side effects, we decided to make this a pilot study rather than a double blind investigation. In all patients the initial dosage of 25 mg. b.i.d. was gradually increased for 6 days until a level of 50 mg. q.i.d. was reached. At that time the effects of the drugs were evaluated, both in regard to tranquilization and side reactions, and the individual dose was accordingly adjusted either in a downward or upward direction. In some patients the dosage was progressively raised until a maximum of 100 mg. t.i.d. was attained. The final dosage varied from 100 to 300 mg. per day, and most patients were receiving 200 mg. per day by the end of the investigation. The entire period of drug administration was 23 days and

each patient was maintained on the maximum individually tolerated dose for a minimum period of 10 days. In addition to daily rounds, a final evaluation of the effects of the drug was made on the last day of treatment. The patients were again evaluated 10 days after the discontinuation of medication. In addition to behavioral changes, other observations were made, including blood pressure, heart rate, and the weight of the patients. The results of electroencephalographic examinations will be reported elsewhere (3).

RESULTS

The most prominent effect of BAS exhibited by the majority of the patients was tranquilization or sedation. This included a decrease of hyperactivity, aggressiveness, irritability, and hostility. Such favorable results were displayed by 14 of the 24 patients at a dosage level of 50 mg. q.i.d. At the end of the study when all patients had been on the maximum tolerated dose, these improvements were shown by 20 patients. Although two of the remaining patients were not considered tranquilized during the period of drug administration, when they were examined 10 days after discontinuation of the treatment, they were found to be more hyperactive and aggressive than when taking the medication. Two other patients, one hebephrenic and one paranoid, were obviously rendered more disturbed by BAS.

In the paranoid patients, the delusional thought production was obviously abated by the drug. The delusions became less important to the patients. Though they no longer excited the usual violent emotional reactions, questioning revealed that they were still in existence and with sufficient provocation it was possible to stir them up. However, in one patient the delusions seemed to have disappeared to such a degree that upon the direct mention of it (a paranoid construction of persecution by a crime ring) the patient laughingly said that she no longer believed such nonsense.

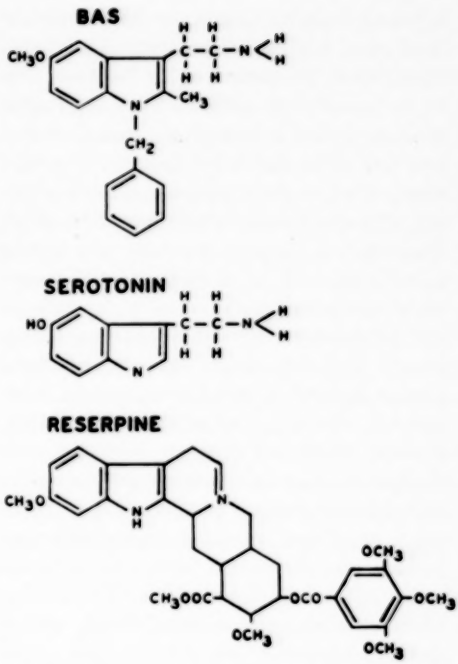

FIG. 1. Structural formulas of BAS, serotonin and reserpine.

The majority of our paranoid patients were suffering from hallucinatory experiences of various types. They complained of somatic symptoms and of bodily changes due to extrasensory influences or auditory hallucinations. In many cases the results of these hallucinatory experiences were readily observed, since they determined such typical behavior habits as the wearing of cotton or paper ear plugs. The removal of the ear plugs was consistent with other signs of improvement.

During the administration of BAS the intensity and frequency of the hallucinatory experiences clearly diminished and many patients ceased their spontaneous complaints. On questioning, three patients said the voices had not bothered them for over 2 weeks, and one said that her enemies had "ceased to snipe at her body" for the last 10 days. However, such beneficial changes were not observed in all patients

suffering from hallucinations, and in two of them the symptoms continued unabated throughout the period of medication. The seven hebephrenic patients were dissociated in thought, and in three cases to such an extent that their speech was reduced to a word salad. Four of these patients showed striking changes during treatment with BAS. Their speech became coherent and it was possible to carry on an understandable conversation, which had not been feasible on any previous study with other tranquilizing drugs. Five of these patients exhibited greater interest in ward activities, in occupational therapy, and in the care of their persons. However, even in these patients, thought content and constructive initiative still retained flatness of affect and inappropriate emotional reactions. One hebephrenic patient was unchanged except for sedation and another was made worse. The schizoaffective senile patient revealed only an unspecific sedative effect.

Side Reactions

In contrast to the usual calming action of BAS, 2 of the 24 patients exhibited increased psychomotor overactivity. Perhaps the most important of the undesirable side reactions which marred the salutary psychiatric effects of BAS was the loss of weight exhibited by 18 patients. These losses were greater than 3 pounds in 13 patients and ranged from 2 to 11 pounds. The loss of appetite and disturbances of gastrointestinal functions were not marked and did not seem to be the chief cause for the decrease of weight, which is attributed rather to a profound feeling of ill being and weakness. A second disturbing side reaction was a disorder of coordination and equilibrium. Fourteen patients exhibited signs of ataxia and three of them complained of dizziness. The patients walked with a broad base and sought support from the furniture and walls. The Romberg sign was positive though their reflexes seemed unaffected. Tremors of the hands were not observed in any patient.

The disturbances of the gastrointestinal tract were not prominent. Three patients complained of nausea and one of these three vomited during the first days of the treatment. These symptoms, however, disappeared spontaneously without a reduction of medication. Two patients complained of gas with mild distention, four patients of constipation, and three of increased bowel activity, but only in one case were there frank diarrhea and rectal spasm. Two patients informed us that they had increased frequency of micturition, especially during the night. One had alternate warm and cold spells and eight were cold most of the time with occasional chills. Sleeping habits were not affected to any great degree. Though the majority of the patients slept better during the night only eight took short naps during the day, chiefly at the beginning of the treatment. There were only a few patients who spoke of nasal stuffiness.

During the first 2 days of treatment, three patients developed a mild transitory nonitching erythematous skin rash at the neck, around the waistline, and on the arms. This rash did not last more than 1 day in one patient and 2 days in two others though the medication was not discontinued. One patient developed a severe erythematous papular eruption over the entire body surface including the mucosa of the mouth and conjunctivas. It is doubtful, however, whether there is any connection between this skin manifestation and BAS, which had been discontinued 6 days previously. The skin healed slowly under ACTH treatment.

Blood pressure was significantly reduced in 10 patients. Four of them with average systolic values above 170 mm. Hg revealed decreases between 30 and 50 mm. Hg systolic pressure and 10 to 20 mm. Hg diastolic pressure. Smaller decreases were noted in three patients whose systolic averages were between 150 and 170 mm. Hg. A drop to hypotensive values was observed in only three patients. Their premedication levels, within normal limits, were reduced to an

average of 90 mm. Hg systolic pressure and 50 mm. Hg for the diastolic pressure. The other 14 patients showed either a slight tendency toward a decrease of blood pressure, chiefly systolic, or remained unchanged.

The heart rate had a tendency toward bradycardia in 10 patients, 8 of whom also revealed diminutions of blood pressure. One patient developed extrasystoles of auricular origin, as confirmed by ECG examination. This disorder has persisted after discontinuation of medication and it is impossible to state whether it is an effect of the medication.

Relation of Dosage to Pharmacologic Effects

The degree of tranquilization produced by BAS varied with the amount administered though the optimal values were not the same in the various patients. In some, the patients were tranquilized at dose levels of 25 mg. b.i.d., and in others satisfactory improvement was not noted until a dosage of 50 mg. q.i.d. was attained. Where benefit appeared, the patients experienced a disappearance or diminution of delusions and hallucinations. Those hebephrenics whose verbalized expressions became less dissociated did so between the two above mentioned dosage levels. Patients whose dosage was reduced because of side effects maintained their improvement with the lower dosage, usually of 100 mg. h.s.

The other side effects, such as ataxia, appetite loss, and sense of malaise, were also related to the dosage, becoming worse as the dosage was increased. In the majority of the patients, the dosage had to be reduced to 100 mg. b.i.d. or 100 mg. h.s. because of the side effects and only three tolerated the maximum amount of 100 mg. t.i.d. for more than a few days. The transitory erythematous rashes and sleepiness did not appear to be related to the dose since they disappeared spontaneously even when the medication was not reduced. In view of the fact that in most patients favorable results were noted with levels of from 50 to 200 mg. per day, it is undesirable to exceed such values.

The discontinuation of the drug was invariably followed by a return of the premedication condition. This applies not only to the salutary psychiatric effects, but also to the side reactions. Their rate of disappearance was rapid. Usually within a few days changes were observed, and in some instances, even on the first and second day after cessation of the medication. On an examination 10 days after discontinuation of the drug, practically all of the effects of BAS had disappeared. The pharmacologic actions of BAS noted by us are in agreement with those previously reported by Wilkins and Hollander. (6)

DISCUSSION

The present results disclosed that BAS exerts distinct effects on behavior, a strong tranquilizing action not unlike that of reserpine. Moreover, some of the side reactions reported with reserpine have also been observed with BAS. Like reserpine, BAS may produce ataxia, gastrointestinal disturbances, fall in blood pressure, and weakness. On the other hand, there is a difference in degree between the effects of these two drugs. With BAS, the gastrointestinal symptoms and nasal stuffiness were less prominent, and pseudoparkinsonian tremors of the hand did not develop, though ataxia was more severe. The only difference in kind instead of degree is a loss of appetite in patients on BAS, but that loss is regarded as a reflection of the profound fatigue and weakness exhibited by these patients. The differences between the therapeutic dose and the toxic manifestations were narrower with BAS than reserpine.

The electroencephalographic studies of Rinaldi (3) have also revealed the similarity of the actions of reserpine and BAS. This similarity may be ascribed to the indole nucleus which is contained in the chemical

structures of both medications (Fig. 1). Both agents, therefore, are capable of displacing serotonin from its receptors in the brain. In accordance with recent work on reserpine (1, 5) not only the serotonin stores, but also those of adrenaline and noradrenaline are released. The differences between the drugs, however, may be due to their nonindolic moieties.

SUMMARY

The effects of BAS, the benzyl analog of serotonin, were studied on 24 chronic, moderately disturbed female psychotic patients. The most prominent beneficial action, that of tranquilization, was noted in 22 of these patients. Tranquilization was attained at dosage levels varying between 50 to 200 mg. per day. The maximum tolerated dose was 300 mg. per day. Among the paranoid patients who improved, the delusions became less important. The intensity and frequency of the hallucinatory experiences diminished. In hebephrenic patients, speech became less dissociated. These salutary psychiatric effects, however, were marred by untoward reactions involving the general health of some patients who lost weight chiefly because of a profound feeling of weakness and fatigue. Another disturbing side reaction deserving comment is ataxia which was extensive in some patients. The effects of BAS are compared with those of reserpine which they resemble in many ways, but are not seen to the same extent with both drugs. The clinical similarities of BAS and reserpine are ascribed to the indole group, which their chemical structures have in common. Their different nonindolic moieties are regarded as being the causes for the clinical dis-similarities exhibited by these two drugs.

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STUDIES ON THE 5-HYDROXYTRYPTAMINE (SEROTONIN) CONTENT IN HUMAN BRAIN[1]

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Although direct evidence of the mechanism by which 5-hydroxytryptamine (serotonin) can be correlated with normal and abnormal mentation processes is lacking, several authors have speculated on its physiologic role (14, 19). Data obtained by previous workers have demonstrated the presence of serotonin in the brain of animals (1, 2). Among the tranquilizing drugs, reserpine has been found to deplete animal brains of their serotonin content (15). Furthermore, both reserpine and chlorpromazine have been shown to antagonize the serotonin evoked contractions of the spayed rat uterus (5). Hallucinogenic drugs like LSD and mescaline have a selective affinity for serotonin receptors of smooth muscles *in vitro* (5), and *in vivo* a serotonin-like activity has been demonstrated on blood pressure (16), as well as on the electric activity of the brain of the conscious cat (4) and albino rat (18). Although serotonin itself was not able to produce a clear and specific behavioral change when injected in large amounts (17), the methylated compound, bufotenin, evoked the appearance of clear LSD-like symptoms in the monkey (7) and man (8). One possible explanation of this reaction is the fact that the enzyme monoamine oxidase, which destroys serotonin rapidly (7, 17), is almost inactive against bufotenin (11). Another factor which might account for the lack of behavioral changes after serotonin injection is the possible impermeability of the blood-brain barrier to this neurohormone (19). However, Feldberg and coworkers (9) have shown that when a direct injection of serotonin is made into the cerebral ventricles changes in behavior do occur.

It is now known that mammalian brain contains serotonin, and a topographic quantitative analysis is available for cat, dog, and rabbit brain (1–3). To the authors' knowledge, no information has been presented on the serotonin content of the many discrete areas of the human brain. It is felt that not until such data are accumulated can analogies be made between animal and human brain studies. Therefore, a preliminary report of the serotonin content of 28 specific areas of the human brain is presented.

METHODS

The serotonin content of the human brain parts was determined by employing spayed rat uterus according to Garven's (10) modification of Gaddum's technique (1). This method permitted the evaluation of the serotonin content without interference from epinephrine. Immediately after the removal of the organ from the skull, the brain was transferred to a 4° C. cold room where the dissection was performed. As soon as the parts were separated, they were immediately frozen between two pieces of dry ice and stored at −20° C. The maximum storage time was 48 hours. As pertinent data on the patients studied, the cause of their hospitalization and the anatomic findings responsible for death are appended.

The time between death and the freezing of brain parts varied throughout the experiments. In H_1 it was 4 to 6 hours, while in H_2, H_3, H_5, and H_6, it was 2 to 3 hours. In H_4 the time was 1 to 2 hours.

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TABLE 1

Serotonin Content of Human "Cortex"
(μg./gm. of fresh tissue)

Isocortex

	H_1	H_2	H_3	H_4	H_5	H_6
Frontal cortex	0.01	0.01	0.02	0.03	0.03	0.02
Gray matter of frontal cortex	—	—	—	0.03	0.03	0.08
Frontal pole	—	0.01	0.01	0.01	0.01	0.03
Temporal pole	0.01	0.04	—	0.07	0.02	0.03
Occipital pole	—	0.01	0.01	0.01	0.02	0.05

TABLE 2

Serotonin Content of Human "Cortex"
(μg./gm. of fresh tissue)

Allocortex

	H_1	H_2	H_3	H_4	H_5	H_6
Cingulate gyrus	—	0.10	0.04	0.04	0.06	0.05
Hippocampal gyrus	0.16	0.30	0.10	0.20	0.13	0.10
Uncus	—	0.30	0.18	0.24	0.16	0.22
Sub-callosum gyrus	—	0.29	—	0.22	0.14	0.60
Anterior perforated substance	—	1.04	1.02	1.51	0.45	0.89
Hippocampus	—	0.06	0.07	0.07	0.05	0.19

RESULTS

The concentrations of serotonin in different parts of the cortex from six human brains are summarized in Tables 1 and 2. It is to be noted that all the structures of allocortex contained greater concentrations of the neurohormone than the isocortex. Especially evident are the high values in the anterior perforated substance. Furthermore, the serotonin concentration of the uncus, hippocampal gyrus, and subcallosum gyrus was also higher than that of the remaining parts presented in these tables.

TABLE 3

Serotonin Content of Neo- and Paleostriatum of Human Brain
(μg. gm. fresh tissue)

Neostriatum

	H_1	H_2	H_3	H_4	H_5	H_6
Putamen (A)	0.46	0.31	0.95	0.85	0.57	0.30
Nucleus caudatus (B)	0.41	0.54	0.35	0.46	0.20	0.70
$\frac{A+B}{2}$	0.44	0.42	0.65	0.66	0.38	0.50

Paleostriatum

	H_1	H_2	H_3	H_4	H_5	H_6
Globus pallidus	—	0.10	0.18	0.73	0.16	0.19

This difference cannot be related to the relatively greater amount of gray matter in these parts because thin slices of gray frontal cortex (Table 1) exhibited the same serotonin content as a complete sample of the same region containing both white and gray matter. Furthermore, the samples of the isocortex processed with Garven's technique (10) did not contain any substance inhibiting the contractions of the rat's uterus because the responsiveness of this organ to serotonin did not change when the tissue extract had been added just prior to the standard.

In Table 3, data are reported for the serotonin content of the neostriatum and paleostriatum. One notes that there is a distinct difference in these data: except for H_4 the results in the neostriatum are considerably higher than those in the paleostriatum.

The data in Table 4 present the serotonin content of 15 cerebral areas mostly nontelencephalic. The hypothalamus, the area postrema, the substantia nigra and in general the areas associated with autonomic activity have a higher content of serotonin than the other areas presented in this table. Such distribution also seems to exist in the dog (1). In one patient (H_6) the serotonin content of locus coeruleus and red nucleus was studied and found to be high: 1.38 and 2.88 μg. per gm., respectively. The callosum and the fornix of man, which essentially consist of white matter, have demonstrable concentrations of serotonin. The cerebellum of man like that of the dog contains very small amounts of serotonin. In this structure, the analysis of the serotonin content was not very easy because of the possible interference of an unknown factor which often changed the sensitivity of the isolated uterus.

In Figure 1, a summary of the results is presented; the concentrations of serotonin

are indicated (as well as in the tables) per gram of fresh tissue as the creatinine sulfate salt.

Case Histories

H_1. F. G., age 73, hospitalized, in 1949, for chronic alcoholism with a delusional confabulating syndrome. In May, 1956, he was found to be well oriented; coherent memory for remote as well as recent events was good. No hallucinations or delusions were present. The cause of death was a severe atherosclerosis of coronary arteries with a fresh thrombotic occlusion of anterior descending branch. The patient died suddenly at 1:05 p.m. on July 17, 1956.

H_2. R. N., age 72, hospitalized, in 1948, for involutional melancholia, arteriosclerosis, chronic alcoholism, alcoholic deterioration. He received chlorpromazine until 24 hours before his death. The cause of death was acute bronchopneumonia, carcinoma of the stomach with metastases and extreme cachexia. The patient died at 7:23 a.m. on August 2, 1956.

H_3. P. G., age 57, hospitalized, since 1929, for dementia praecox of hebephrenic type. Received reserpine (2 mg. per day for 3 days) 8 days before his death. The cause of death was marked atherosclerosis of the coronary arteries with occlusion of the left coronary vessel. Infarcts of the lungs were also present. He died at 9:05 p.m. on August 2, 1956.

H_4. H. R., age 69, hospitalized, since 1952, for psychosis with cerebral arteriosclerosis on July, 1956. The patient was in good contact and oriented but he was easily irritable and constantly hostile. The cause of death was malignant metastatic neoplasm of the stomach for which he had been operated on July 26, 1956. Before the death he received Demerol. The patient died at 8:45 a.m. on August 13, 1956.

H_5. B. O., age 62, hospitalized, since 1937, for psychosis with mental deficiency. Cause of death was cerebral hemorrhage, arteriosclerosis. A few hours before death she had received Dilantin (90 mg. by mouth). She died at 3:00 p.m. on October 6, 1956.

H_6. P. D., age 81, hospitalized, since 1953, for senile psychosis. He was a quiet and cooperative patient. Delusions and hallucinations were not elicited. Cause of death was bronchopneumonia, arteriosclerosis, cancer of the pancreas with liver metastases. Before death he had been given antibiotics. The patient died at 7:33 a.m. on November 8, 1956.

TABLE 4

Serotonin Content of Human Brain
(*μg. gm. of frozen fresh tissue*)

	H_1	H_2	H_3	H_4	H_5	H_6
Fornix (anterior pars)	—	0.46	0.50	0.55	0.22	0.06
Corpus callosum	—	—	0.20	0.35	0.39	0.05
Amygdaloid nucleus	—	0.33	0.22	0.67	0.24	0.14
Thalamus	0.23	0.62	0.25	2.70	0.26	0.30
Hypothalmus	0.32	1.53	0.67	1.31	0.49	0.57
Mammillary bodies	—	—	—	0.48	0.27	0.43
Anterior quad. bodies	—	—	—	1.02	0.90	0.50
Posterior quad. bodies	—	—	0.42	0.81	0.34	0.29
Substantia nigra	—	—	—	1.96	1.11	1.20
Pons	—	—	0.52	—	1.03	0.55
Medulla oblongata	0.48	0.29	0.35	0.50	0.20	0.24
Area postrema	0.51	—	0.81	0.42	0.68	0.43
Cervical spinal cord	0.21	0.09	0.19	0.11	0.10	0.13
Cerebellum	0.01	0.01	0.03	0.02	0.09	0.04

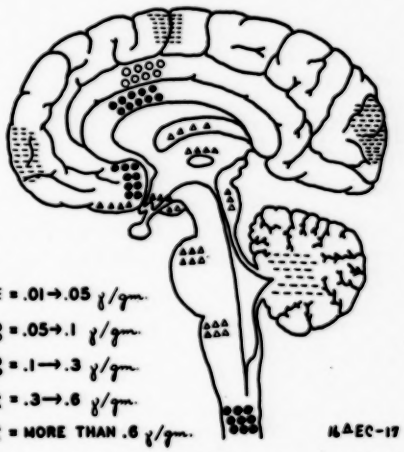

FIG. 1. Serotonin content of human brain. (*1*) Frontal cortex; frontal pole; occipital pole; cerebellum; (*2*) cingulate gyrus; (*3*) subcallosum gyrus; cervical spinal cord; corpus callosum; (*4*) medulla oblongata; posterior quadrigemina bodies; pons; mammillary bodies; thalamus; fornix; (*5*) anterior perforated substance; hypothalamus; anterior quadrigemina bodies.

DISCUSSION

We believe these results present the first direct evidence for the presence of 5-hydroxytryptamine in the central nervous sys-

tem of man. From the data presented in Tables 1 and 2, high serotonin contents can be used to distinguish biochemically isocortex from allocortex. This distinction brings chemical evidence in good agreement with the different morphologic and phylogenetic characteristics of these two contrasting areas. Evidence (6) of a preliminary nature suggests that serotoninase is present in human cortex. An explanation for these chemical differences would be obtained if the concentrations of serotoninase were lower in the allocortex than in the isocortex. However, at present, the details of the micromethod for the quantitative determination of serotoninase activity in brain homogenates have not been completed.

Two of our patients, H_3 and H_5, received treatment with reserpine and Dilantin, respectively, before death. Probably the amount taken and the interval of time were not adequate to influence, significantly, the brain serotonin concentrations.

Speculation on the importance of the serotonin in normal human brain processes is not possible because at present only brains of mentally ill patients have been analyzed. Additional complications include: (*a*) delay of time between death and autopsy, (*b*) cause of death and (*c*) possible variations in serotoninase activity caused by the use of drugs in the patients studied. Nevertheless, the limbic system which is concerned with the experience and elaboration of emotion (13) as well as the orbital region of the cortex from which (area 12) the corticohypothalamic fibers seem to emanate (12) both have higher concentrations of serotonin than other telencephalic areas. Even if it is not possible to establish the pathophysiologic meaning of the indole compound in the brain, the evidence that it is present serves as a basis for further development of our knowledge. It is now necessary to determine whether a correlation exists between the serotonin content of the brain and mental behavior.

SUMMARY

The presence of serotonin in human brain structures has been demonstrated. The areas of the allocortex had higher serotonin concentrations than the isocortex. The highest concentration of serotonin per unit weight of tissue is in the mesencephalic structures (mainly substantia nigra and probably red nucleus); the diencephalic structures (hypothalamus) contain also relatively large amounts of this neurohormone. The cerebellum as well as the isocortex have the lowest concentrations of serotonin.

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EXCHANGE TRANSFUSIONS IN SCHIZOPHRENIC PATIENTS[1]

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For the past half a century, ever since Kraepelin (9) delineated the then confusing term *dementia praecox*, medical science has attempted to determine the etiology of this disorder. Since this time, a variety of etiologies has been presented, discarded, rediscovered and re-presented. There have been waves of interest in various aspects ranging from the completely psychogenic to the completely organic, with others attempting an amalgam of varying concepts. The difficulties involved in this endeavor are well illustrated in the appendix to Bellack's textbook, *Dementia Praecox*, (3). There, under eight headings, he lists 39 different etiologic factors of dementia praecox.

Recently, under the impetus of the discovery of the tranquilizing drugs, there has been a reappraisal of many of the organic factors in the etiology of schizophrenia. Attention has been particularly centered about the possibility that a circulating protein, most likely an abnormal breakdown product of a normal constituent of the body or blood stream, may be responsible for the development and maintenance of the symptoms of schizophrenia. The Tulane Group directed by Heath (6) has recorded isolation of such a substance, termed *taraxein*, which when injected in voluntary controls produced the symptoms of schizophrenia in 21 instances. Hoffer *et al.* (8) have held that an abnormal intermediate breakdown product of adrenaline may well be responsible for the symptoms of schizophrenia.

When one contemplates the many possibilities concerned in what we might term the toxic origin of schizophrenia one of the simplest would be that an abnormal substance derived from a normal bodily metabolite is responsible not only for the production but for the elaboration of the schizophrenic symptoms. This hypothesis is suggested by the above mentioned work. It must be emphasized that this is the simplest thesis—that many more complicated ones might be envisaged. Thus, while the toxic substance might be present at the time of the original development of the symptoms, the disorder might well be perpetuated long after the abnormal metabolite has disappeared. However, a very reasonable method of approach in this very difficult field would be to take the simplest hypothesis, subject it to experimental scrutiny, and if the hypothesis is proved invalid go on to a more complex one.

We have, therefore, elected to test the hypothesis that a protein circulating in the blood is responsible for the production and maintenance of the symptomatology of schizophrenia. It would follow that if such a substance is removed from the body a temporary remission should take place. This is a situation that is not uncommon in the field of pediatrics. For example, in erythroblastosis fetalis a substance normally in the body, bilirubin, is present in the circulating blood stream in excess amounts. This substance has been shown to be toxic (2, 5). Since the bilirubin might contribute to the production of irreversible brain damage or possibly death, one should remove the bilirubin. By means of exchange transfusions this problem has been solved (1), and in this way significant amounts of bilirubin can be washed out of the body. The damage that might otherwise ensue can be minimized. Similar methods have

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been utilized in the treatment of children who have been poisoned by boric acid (4).

It, therefore, occurred to us that such a method might be useful in the testing of the above hypothesis.

A survey of the literature indicated that we were not the first to whom such an idea occurred. Reiter (12), in 1938, reported exchange transfusions in four schizophrenic patients, three of whom displayed temporary remissions. It is noteworthy that of the three patients showing improvement, two displayed impressive change. In these cases, the remission lasted from three to four weeks. On the other hand, Pfeffer and Pescor (11), in 1944, reported on the effect of multiple transfusions in six schizophrenic patients. It must be noted that instead of large exchanges done in one procedure, such as Reiter reported, Pfeffer and Pescor withdrew 500 to 1000 cc. of blood and injected an equivalent amount daily or every other day over a considerable period of time. Only one patient in Pfeffer and Pescor's series of six showed any change which could not be unequivocally related to the exchange.

In addition, the experiments of Goldbladt and Krapiwkin (7) may be cited. They administered single transfusions to 12 schizophrenic patients. Their source of blood was from normal and schizophrenic subjects in remission. Eight of the 12 demonstrated improvement. Three of these were stated to have demonstrated complete recovery.

Pascal and Davesne (10) administered whole blood to six patients; however, they used the intramuscular route. Five of the patients improved. Two of them were described as recovered.

In view of the contradictory results, it appeared worth while to repeat this work, utilizing our more modern skills in performing exchange transfusions.

This project was embarked upon not as a means of discovering a new therapy, because at best only temporary remission could be obtained, but as a means of testing a hypothesis which would not only clarify investigation but might also lead to further discoveries.

METHOD

The subjects for this study consisted of four patients. One was a five and one-half year old autistic child; the other three were adults.[4] The history of each will be given below. Only local anesthesia was used. Tranquilizing drugs were discontinued one month and other medications one week before the transfusions. Blood of the proper type was obtained during the previous 24 hours from subjects who were physically in good health and gave no history of mental illness.

In the case of the child, a cutdown was performed on one of the antecubital veins. A No. 7 polyethylene catheter was inserted into the vein and connected by means of a three way stopcock to a syringe and to a bottle of blood. Thus, the blood could be drawn out of the vein and then the flow reversed and blood pumped back into the body by means of the syringe.

In the case of the adults, no cutdown was necessary. Needles were inserted into both antecubital veins. Usually 500 to 1500 cc. of blood were first drawn off to be saved for future studies. Transfusion was then begun on the opposite arm and blood continued to be drawn off in 500 cc. allotments. Inflow and outflow of blood were matched. Intravenous Benadryl was available for the treatment of sensitivity reactions to transfusion. In addition, Demerol was administered in each case late in the procedure for discomfort. In one case (Case 3, *see below*), the antecubital veins were not satisfactory; puncture of the femoral vein was done through the skin under local anesthesia.

[4] Doctors Nathan Beckenstein, James Rappa, and Joseph Villara of Brooklyn State Hospital and Doctor Lisbeth Sacks of Kings County Hospital were most helpful to the authors in carrying through this project.

CASE HISTORIES AND RESULTS

Case 1. Stuart was a 5½ year old boy, one of identical twins. His twin, Thomas, was also available for study. There was no history of mental illness in the family. This was the second pregnancy for the mother. Pregnancy and delivery were stated to have been normal. Stuart weighed 7 pounds at birth, whereas the twin brother, Thomas weighed 6 pounds. Stuart was born first. In their early development, it was noted that both children were quite unaware of their parents. The mother described both twins as living in a world of their own. In later development, Thomas began to display some attention to other people, but Stuart continued to be remote. In addition, Stuart cried a good deal as an infant, was very impulsive, and had a bad temper. He was also given to wild and destructive activity. Both twins sat up at 6 months, got their first teeth at 8 months, and stood at 1 year. There is uncertainty concerning the age at which they could walk without support. The parents estimate it at 18 months. They were not toilet trained until they were over 4 years old. Stuart rocked his bed going to sleep until he was 1½. Since the age of 2 he had been a head banger. Stuart had excessive fear of riding in a car or in a bus. He had sleep disturbance which the parents attributed to dreams. Stuart always played alone. Thomas would play on occasion with his older sister. Stuart was fond of music and responded when his mother picked him up and danced to radio music.

On psychologic testing, Stuart's "inability to speak and his poor cooperation did not permit an accurate assessment of his intellectual abilities and he is therefore unclassified." At the time of testing, Stuart was retarded by 1 year on the Vineland Social Maturity Scale. At the same time, Thomas was up to age, on the same test.

At the time of study, Stuart was completely mute and did not babble. However, the mother did recall that at the age of 4, Stuart did say hello on the telephone. From the age of 4, Thomas had been babbling, made attempts to speak, and had exhibited echolalia. Both children were diagnosed as having childhood schizophrenia of the autistic type.

Both Stuart and Thomas were hospitalized for the purposes of this study. Since Stuart was the sicker of the two, the exchange transfusion was performed on him, while Thomas was kept as a control.

After a preliminary study of both these children in the hospital, an exchange transfusion was performed on Stuart in the operating room as described above: 1400 cc. whole blood were drawn off and an equivalent amount injected. It was estimated that an exchange of 55 per cent had been performed. In the early part of the transfusion, Stuart was quite restless. However, as time went on, he became particularly tranquil and unperturbed. This was noticed even before some chilling necessitated the injection of Demerol. Postoperatively, Stuart had a temperature of 101° F. for 1 day. He was placed on a regime of antibiotics immediately after the transfusion. Aside from this, physical recovery was uneventful.

Certain changes were noted in Stuart that were not obesrved in Thomas. Stuart showed more awareness of the examiner. Instead of being completely oblivious of the examiner, he would reach out his hands and touch the examiner's lips when the latter was talking. He also pulled at the examiner's ears. When visits were made, he would run over to be picked up. He began to enjoy playing simple games. If placed on a high perch, he would jump down into the examiner's arms. Also for a period of 2 weeks following the transfusion, Stuart babbled. Thereafter, the babbling slowly disappeared. Certain changes occurred in both Thomas and Stuart, such as improvement in toilet habits, that could be ascribed to hospitalization or maturation.

Three weeks after the transfusion, Stuart and Thomas were discharged from the hospital. The parents who had visited Stuart regularly during the hospitalization felt that he had demonstrated a greater spurt than Thomas. Two weeks after discharge, they stated that Stuart was pretty much as he had been before the procedure and had "slipped back." Thomas continued to mature slowly. There were no physical sequelae.

Case 2. Leo was a 45 year old man. Family history was said to be negative for mental and nervous disease. The patient was the youngest of 11 children. He was a blue baby but was resuscitated by the midwife. Childhood development was said to be not remarkable.

There was close attachment to mother and sister. School was begun at the age of 6. He was very poor in school and only reached grade 5B at the age of 17. He had temper tantrums and was very stubborn as a child. If frustrated, he would strike himself or would bite his arm. At puberty, he became extremely seclusive. He would sit around the house brooding. He was shy and very isolated.

At 21, he was admitted to a state hospital with a history of having been peculiar for the previous 2 years. He was extremely seclusive, resented any interference and became irritable. He showed a tendency to smile, mumble, and gesticulate to himself. He was slovenly in his habits and felt neighbors were laughing at him.

Shortly thereafter, he was transferred to another hospital with the diagnosis of dementia praecox of the hebephrenic type. One year later he was paroled and was discharged 1 year later as improved.

During the interval, he never did well, would have violent spells, yell and curse while the family ate. He was slovenly and unclean. He was hospitalized again 7 years later. Leo was again diagnosed as hebephrenic, dementia praecox. His physical examination at this time was negative. He was talkative, rambling, and illogical. He was not overactive. Emotionally, he was shallow and at times silly. He denied hearing voices or having any hallucinations, but he displayed peculiar postures of hands and arms. This was especially noticeable when he spoke. Recent and remote memory were poor. Orientation was fair and abstract conceptions and general knowledge were poor. He was described as sloppy and untidy, deteriorated, confused, and out of contact. There was little change in his status.

One year later, 20 electric shock seizures were induced. He remained essentially unchanged, continuing to be disheveled, dirty, restless, impulsive, and probably hallucinating. He seemed completely preoccupied. During the ensuing year, the patient received 10 occasional shock treatments. In 1947, at the age of 35, 16 grand mal seizures were induced with Metrazol, but since behavior became worse, the therapy was discontinued. He remained dirty, incontinent, untidy, impulsive, and self-punishing. The deteriorated state continued until 1950, when 20 electric shock treatments were administered. Condition at the end was unimproved.

Prior to the transfusion, Leo was unable to contact his surroundings or even answer simple questions. He was stated to be inappropriate, detached, incoherent, and paralogic. He was possibly hallucinating. Most questions were answered with, "I don't know." Sensorium was questionable No insight or judgment was present. He was untidy, regressed, and idle.

The patient was cooperative throughout the procedure. Initially, 1500 cc. of whole blood were withdrawn from one cubital vein; 1500 cc. of whole blood were then transfused via the other arm. Thereafter, intake and outflow were kept as identical as possible. In all, 4500 cc. of whole blood were drawn off and 4550 cc. injected. It was estimated that 57 per cent of the patient's blood was exchanged. The procedure was terminated because of urticarial wheals which broke out over the chest and body. During the middle of the procedure, Leo became particularly peaceful and tranquil. The continuance of this state could not be properly evaluated. Later, it became necessary to inject intravenous Benadryl and Demerol because of the reaction he exhibited. Following the procedure, Leo was placed on a schedule of antibiotic therapy. There was a 3 day febrile reaction. During this time, he remained disoriented and confused. He answered questions by repetitiously asking, "When is visiting day?" He did inquire concerning his relatives which he had not done before. However, in general, his reaction was essentially unchanged.

Case 3. Harry, a 25 year old male, was first hospitalized when he was 18 years old. Family history was negative for mental and nervous disease. Pregnancy and delivery were normal. There were no feeding problems or toilet training problems described. The patient had the ordinary diseases of childhood and scarlet fever at 5 years of age. He was described as a bashful boy who had great difficulty making friends. He was very much attached to his older brother, was withdrawn, and spent a lot of time reading books. He felt that the world did not want him. He never made dates with girls but was described as enjoying looking at pictures of girls in bathing suits. He was not close to his father.

Two weeks prior to admission, patient had a wisdom tooth removed. After this, he com-

plained of terrible headaches, which were treated by a physician. He began to stay up nights and make funny faces. He complained that no one would give him a break.

At admission, he was physically well developed and well nourished. Physical and neurologic examinations were negative. He appeared to be withdrawn, seclusive, immature, and expressed ideas of influence and reference. He felt that he could not control his thoughts and stated spontaneously that his thoughts were under the control of his mother. He felt unable to make decisions and related auditory and visual hallucinations. He felt that people on the street stared at him and talked about him because of the way he walked. He showed defective insight and judgment.

Several days after admission an evaluation found him as generally depressed and preoccupied. He was noted to stutter and stammer all through his interview and was suspicious of the examiner. He appeared frightened and moved very little during the interview, sitting in a somewhat hunched position. He spoke spontaneously but his thoughts seemed disconnected and irrelevant. He stated, "Sometimes I put another's name in my body. I feel my flesh crumbling; I seem to get smaller. That's because I sin." He was oriented. Sensorium was clear. Insight and judgment were lacking. He was diagnosed as dementia praecox, catatonic type.

Insulin shock therapy was begun and in several months he completed a course of 60 treatments. He showed considerable improvement. He was now described as pleasant and cooperative. He no longer heard voices but still felt that he had been treated unjustly and discriminated against by other patients. He showed no assaultive or aggressive tendencies. He was placed on convalescent status.

He returned from convalescent status 1 year later. He was extremely agitated, accused his mother of making him nervous. However, he denied hallucinations. At this time, he received 20 electric shock treatments in combination with insulin. Slight temporary improvement was displayed. Hallucinations were described and he stated that demons talked to him. He remained apprehensive and tense. He was frequently getting into fights. He stated that he was mixed up in the head. There was marked evidence of ideas of persecution, reference, and influence. Insight and judgment were completely lacking.

Consequently, Metrazol shock treatment was begun. He underwent five major convulsions and was thought to be improved. However, in 2 months, he began hallucinating again and electric shock treatment was begun, consisting of 17 major convulsions. His condition was unimproved.

No significant changes were noticed during the following year. His affect was markedly flat and he was manneristic, grimacing, and twitching. He was confused and had difficulty finishing sentences. He admitted to auditory hallucinations, and some paranoid elements were elicited.

Another course of electric shock therapy and large doses of Thorazine were administered. In neither case was there appreciable change.

In March, 1957, he was described as having blunted affect, circumstantial production. He admitted to hallucinations, hearing voices telling him to go home. He was evasive when questioned about paranoid trends. He was disoriented for time; insight and judgment were lacking.

Upon being brought to the operating room for the exchange transfusion, he had to be restrained because of panic. However, the procedure was performed under local anesthesia; 6000 cc. of whole blood were injected and 6150 cc. were removed. It was estimated that 63 per cent of the patient's blood was exchanged. Following the initial difficulty, the procedure went along smoothly. A period of relative tranquility was noticed in the course of it, which continued until the end of the procedure. For a period of time, during the transfusion, he denied any of the hallucinations which had been present continuously before. However, before the end of the procedure, he again described auditory hallucinations. Following the completion of the transfusion, he was given antibiotics. There was a febrile reaction for 4 days. Repeated interviews with the patient revealed no substantial change in his mental status. Auditory hallucinations continued and he remained suspicious, silly, and inappropriate. It was felt that no significant change had occurred.

Case 4. David was a 28 year old man who was first hospitalized when 23 years old. There was a family history of mental illness. He was the oldest of seven siblings. Eearly childhood was uneventful. He completed the fourth term

of high school. David worked from age 13 at a variety of stores. He was described as "a very nice quiet boy." While a camp counsellor, he began to have nightmares and difficulty with his coworkers. He enjoyed reading science fiction and was said to have been well liked and had many friends. One year prior to admission, he began to complain of nervousness and difficulty at work. At this time, he saw a psychiatrist, who recommended shock treatment. The patient became very fearful about this. Six months prior to admission, he had difficulty sleeping and became very anxious and began to have dreams of being chased.

He was described at admission as being greatly agitated. His speech was blocked and incoherent. He was hostile and suspicious. He demonstrated auditory hallucinations and delusions of grandeur and persecution. His affect was blunted and judgment was impaired and insight lacking. He admitted to auditory hallucinations. He was very threatening and assaultive at admission. After several days he quieted down. However, he admitted to suicidal thoughts and stated that people were against him, particularly his mother and father. He complained of inability to think right and felt other patients were spying on him. He also stated he had fears of dying. He was well oriented and recent and remote memory were adequate. Abstract thinking was good. Insight was superficial and judgment fair. The diagnosis was dementia praecox, paranoid type.

Additional information was obtained from the patient's mother which indicated that his development was normal. He was breast-fed to 12 months. He walked at 1 year of age. He was toilet trained before 1 year. The patient had one accident when he was 10 months old, but there did not seem to be any severe head injury.

Shortly after admission, insulin therapy was begun. During this time, patient was involved in a fight with another patient. He did not respond to insulin therapy. Consequently, electric shock therapy was begun. Following 17 treatments, he was able to go home weekends and was placed on convalescent status and felt to be improved.

He was returned from convalescent status 6 months later because he had been getting worse. He became very tense, complained of headaches, took many cold baths. He would stand in one spot shaking and would not go out of the house. Another course of electric shock therapy was begun. Following this, his affect was described as poor and diminished. There was no gross psychotic thinking. However, patient seemed autistic and somewhat distracted. Sensorium was clear.

While at home, patient thrust his hand through a window and suffered severe lacerations of the wrist. He was withdrawn, tense, and unable to explain his impulses. Home visiting privileges were withdrawn.

For the next year, very little change was observed in him while he remained in the hospital. In July, he was transferred to surgical service because of rectal bleeding. There he was described as neat and tidy although he spent most of the day in the kitchen. He rarely talked to other patients. He was reluctant to be interviewed and there was apparent blocking during interview. His affect was constricted. He seemed generally indifferent toward questions. No delusions or hallucinations could be elicited. Patient had prolonged treatment for the anal fissures and hemorrhoids. Subsequently, he developed an anal stricture which was dilated under anesthesia.

In November, 1956, patient impulsively injured several of the attendants and attempted to strike the doctor on the ward. Patient was given Serpasil and then electric shock therapy. In February, 1957, maintenance treatment was terminated without much benefit. Patient received a total of 19 modified convulsions without any complications. Minimal improvement was noticed.

He was again given Serpasil. Affect remained blunted. He continued to be impulsive. He was evasive when questioned about hallucinations. Sensorium was clear.

Shortly thereafter, an exchange transfusion was undertaken. At the beginning of the procedure, David was relatively cooperative; 1000 cc. of blood were withdrawn at the start. The blood was saved for future study. David was cooperative at first, but became increasingly restless and uncooperative. A total of 3650 cc. of blood were drawn off and replaced by 4200 cc. of normal whole blood. It was estimated that 54 per cent of the patient's blood was exchanged. David was placed on antibiotics and demonstrated a febrile reaction for 2 days. David's

paranoid symptomatology was very much in evidence and became increasingly so on each successive day. He became increasingly suspicious and impulsive. Without provocation, he struck another patient and at another time an attendant and a physician. It was necessary to place him upon maintenance electric convulsive therapy. The response to this was slight improvement.

DISCUSSION

The removal of 54 to 63 per cent of the blood of four schizophrenic patients by exchange transfusions over a 1 to 3 hour period resulted in no changes in the mental condition of three adults. In one child there was a possible slight improvement lasting a few days. We are left, then, without much in the way of support for the humoral theory, in so far as that theory can be tested in this way.

Failure to achieve more decisive results could arise from the following.

1. The humoral theory of the etiology of schizophrenia could be incorrect.

2. The exchange was not complete enough to result in a changed mental condition. It is conceivable that an exchange of the order of 90 per cent might be required to effect such a clinical change.

3. The "toxic" agent may not only be present in the blood, but also saturate the tissues of the body. Thus, as rapidly as it is removed, it is replaced from the tissue. Consequently, it may be difficult or impossible to remove it by means of exchange transfusions.

4. There are somatic changes produced in schizophrenia which are not affected by temporary or partial reductions in the humoral factor.

Regarding the last possibility, it is noteworthy that whatever change did take place occurred in the child. This might suggest that an abnormal metabolite may produce changes which in time becomes irreversible. Further, schizophrenia may well exist from birth. Therefore, this procedure would only yield results within the earlier years, while there would be some opportunity for reversibility. This possibility can only be answered by further experimentation.

However, the question of opportunity for reversibility might be an important one. We have not, as yet, done an exchange transfusion on any patients who are experiencing their first acute breakdown. The onset of David's schizophrenia is given as 5 years prior to exchange transfusion. Harry has been manifestly ill for 7 years, however, Leo has a history of mental illness for over 25 years. There is no difference in the poor response in all three cases.

Reiter (12) did report improvement in 3 of 4 patients who had had illness of long standing. Our results failed to confirm Reiter's findings and are similar to those reported by Pfeffer and Pescor (11). Only 1 subject of their 6 improved. It was noticed previously that their procedure was that of doing small exchanges over an extended period of time. It is noteworthy that the 1 patient who did improve was ill the shortest period of time, 9 months, and received larger transfusions over a shorter period of time than the other cases.

The study indicates, however, that exchange transfusions can be done quite readily and in the hands of alert and skilled personnel without too great danger. It does also afford a means of obtaining large amounts of blood from a single patient which might be useful in further biochemical studies.

A point of intersting comparison between our series and that of Reiter's is the period of tranquility in a number of patients. This may be an nonspecific effect. On the other hand, during a period when a toxic substance is being removed, there may be a latent period before it is replaced from the tissues. This may be reflected in the tranquil period.

Since there was a possible slight effect in the one child, we propose to continue the study using young subjects and more complete exchange.

SUMMARY

1. The hypothesis that a substance circulating in the blood is responsible for the symptomatology of schizophrenia was tested by means of exchange transfusions.

2. The patients consisted of a five and one-half year old autistic child and three chronically ill male adults who had, respectively, paranoid, hebephrenic, and catatonic schizophrenia.

3. The status of the adults remained the same.

4. The child may have improved slightly. The extent of the improvement was not enough to exclude nonspecific factors.

5. The humoral theory is not supported, but neither can it be said to have been invalidated by these observations.

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